FIG. 1

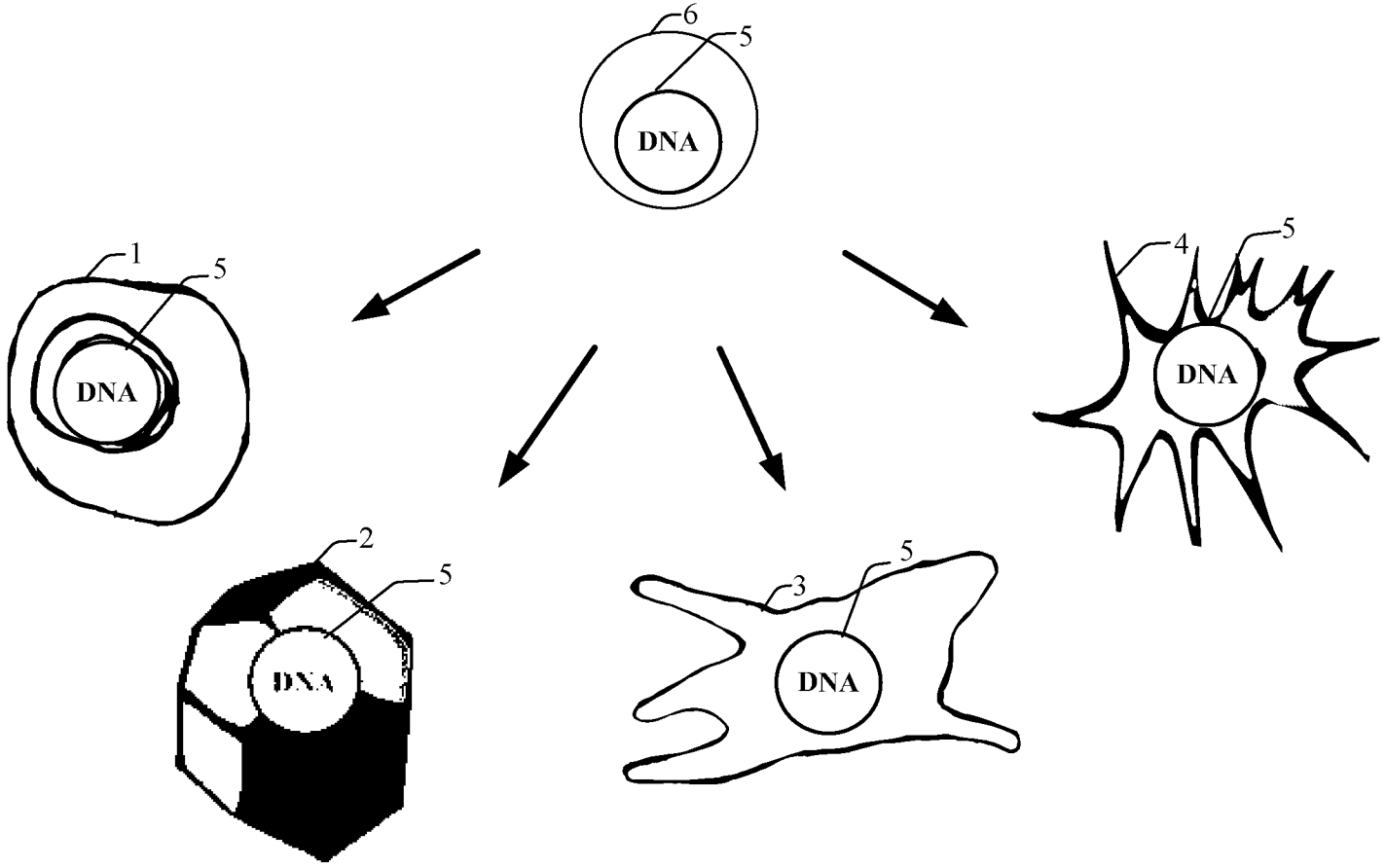


FIG. 2A

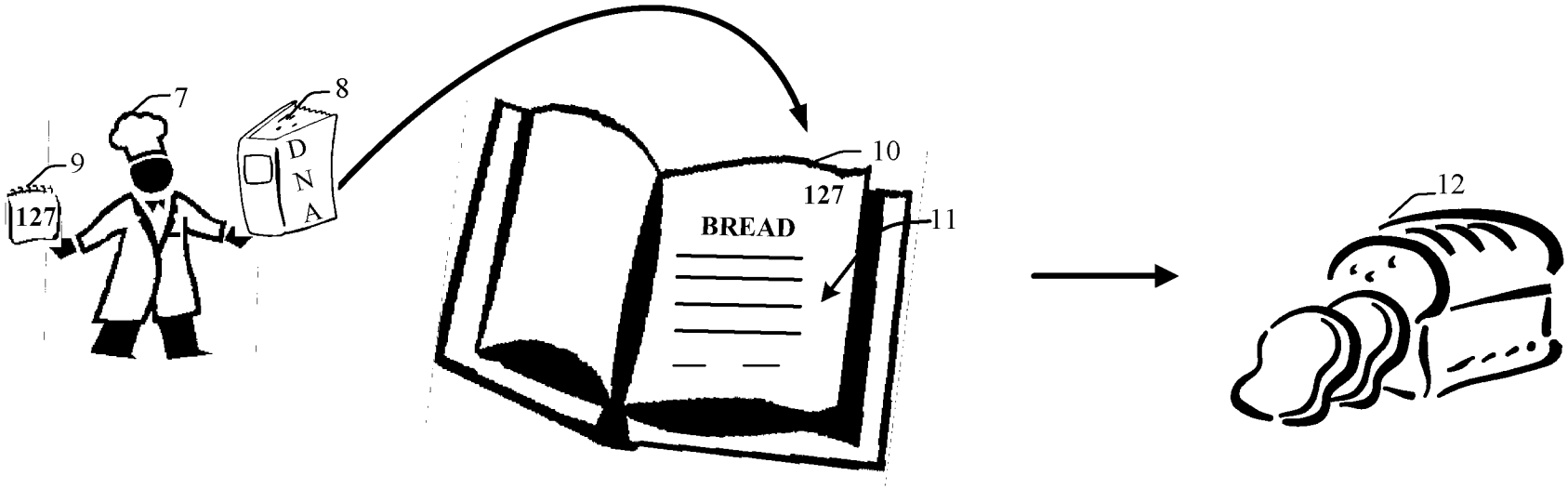


FIG. 2B

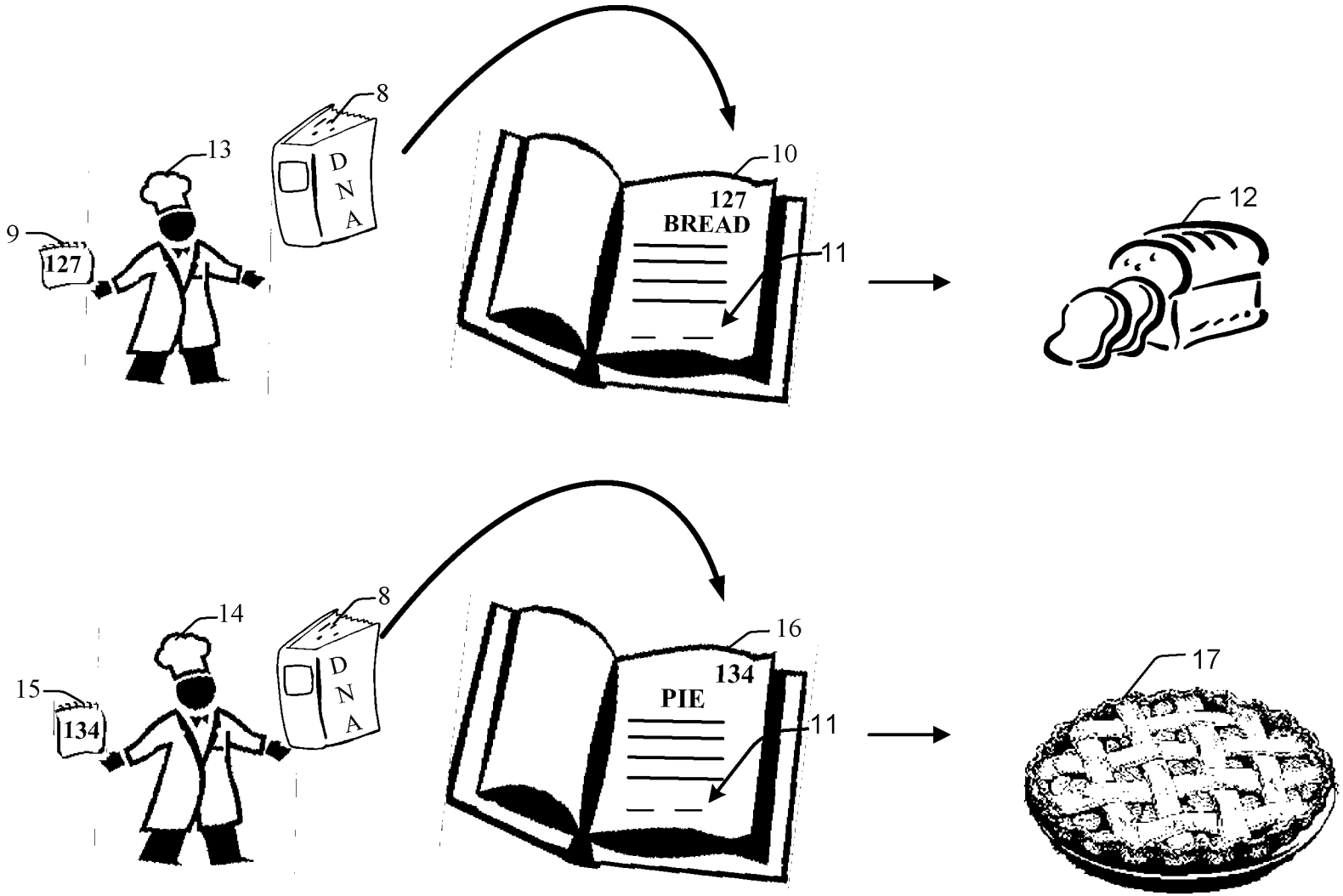


FIG. 3

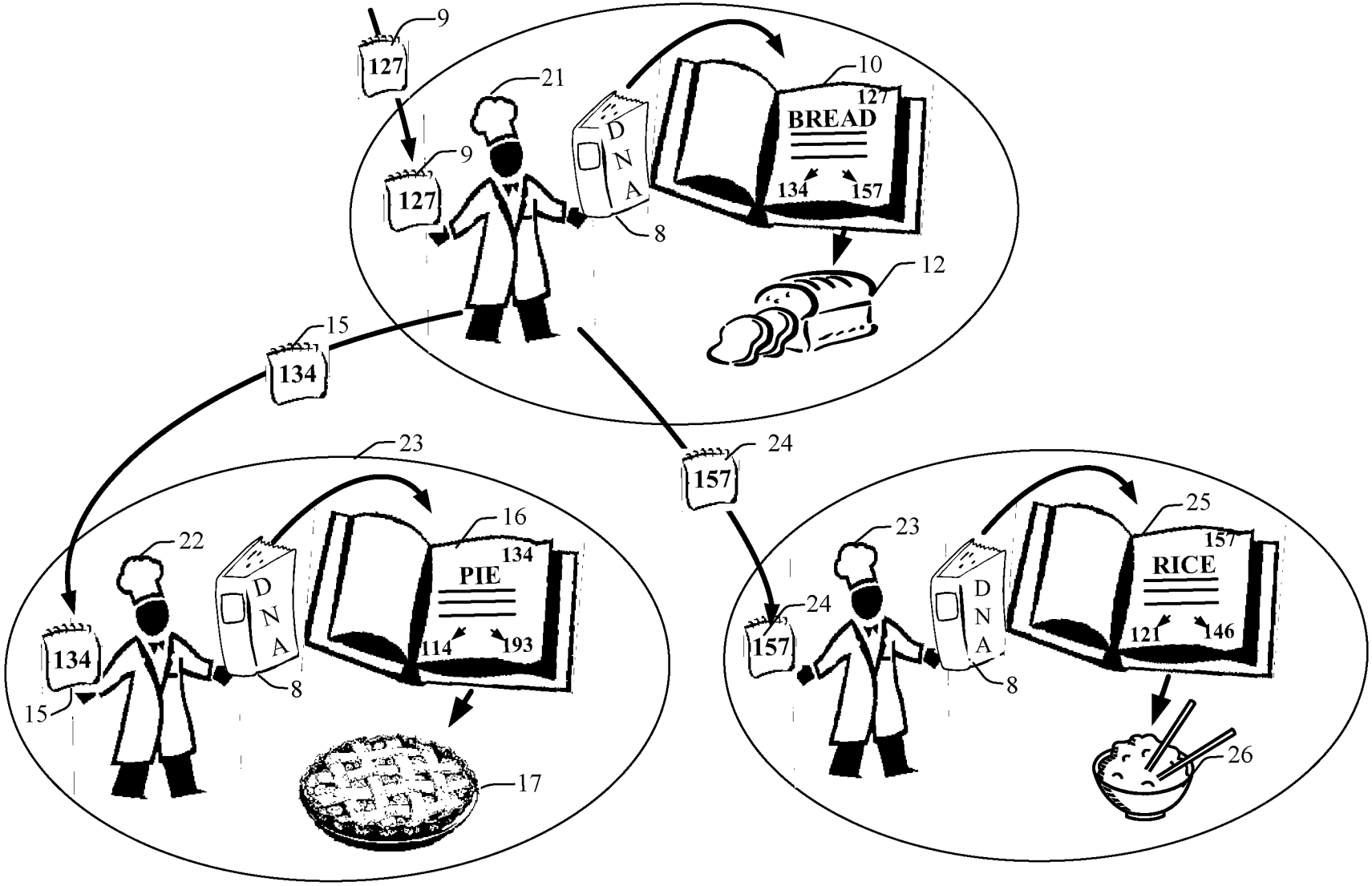

9
127
21
10
127
BREAD
134
157
8
12
15
134
23
24
157
22
16
134
PIE
114
193
8
15
17
23
25
157
RICE
121
146
24
157
8
26

FIG. 4

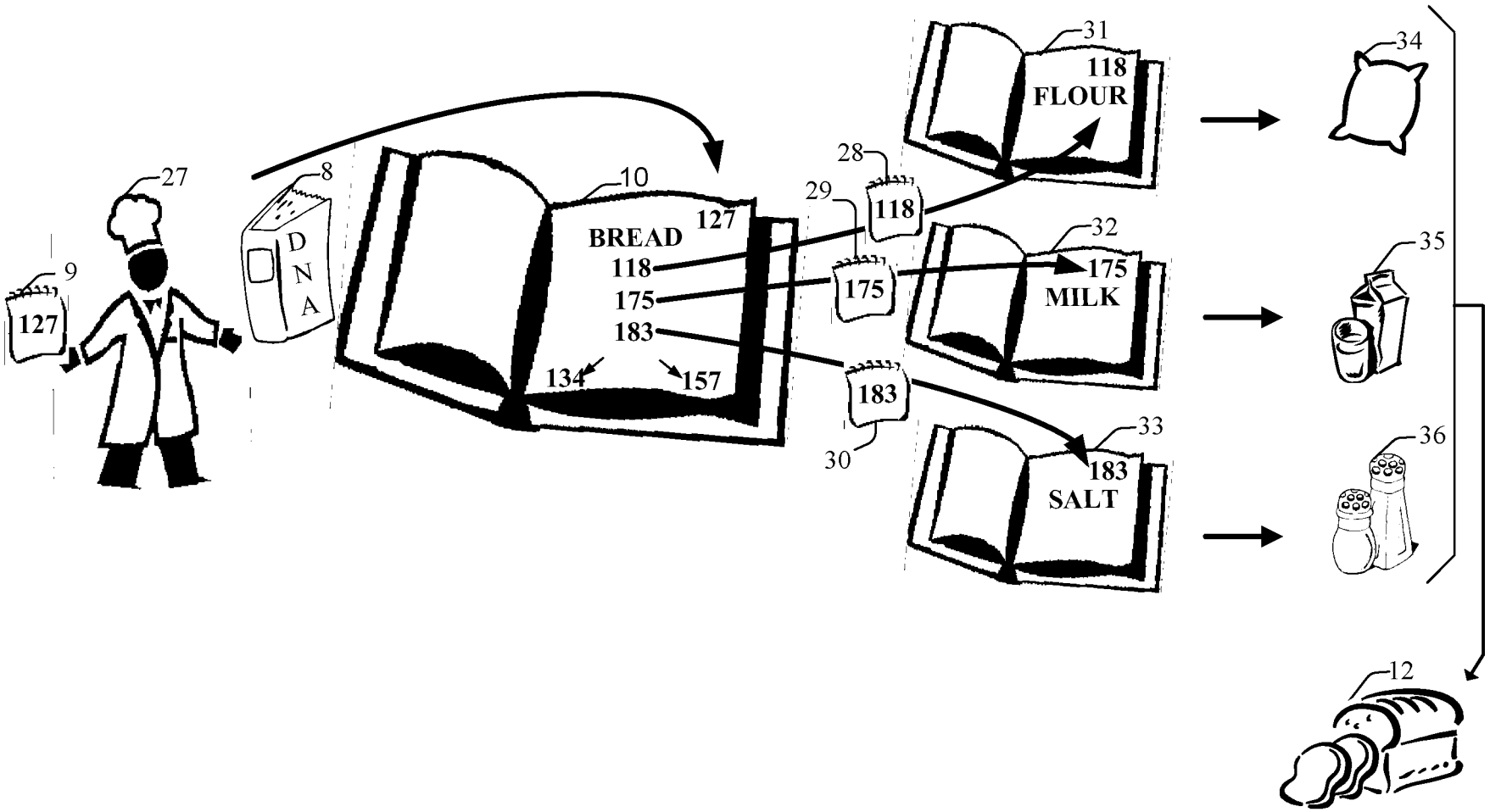

27
8
10
9
127
D
N
A
BREAD
127
118
175
183
134
157
28
29
118
175
183
30
31
118
FLOUR
32
175
MILK
33
183
SALT
34
35
36
12

FIG. 5A

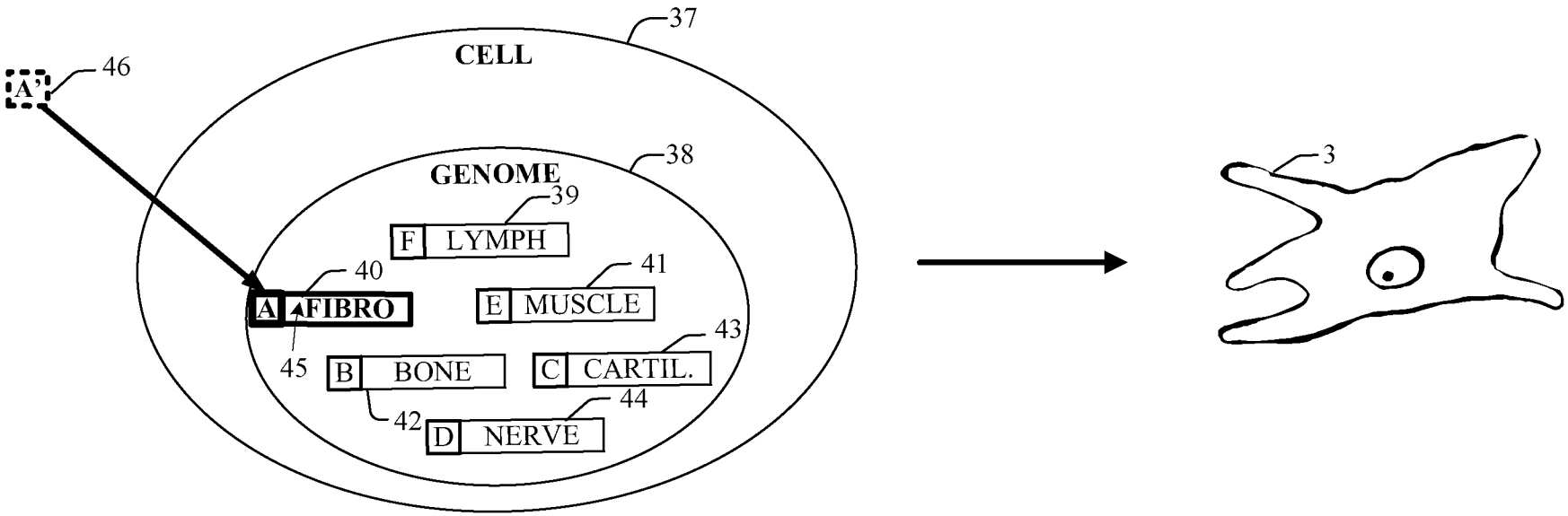

A'
46
CELL
37
GENOME
38
39
F LYMPH
40
41
A FIBRO
E MUSCLE
43
45
B BONE
C CARTIL.
44
42
D NERVE
3

FIG. 5B

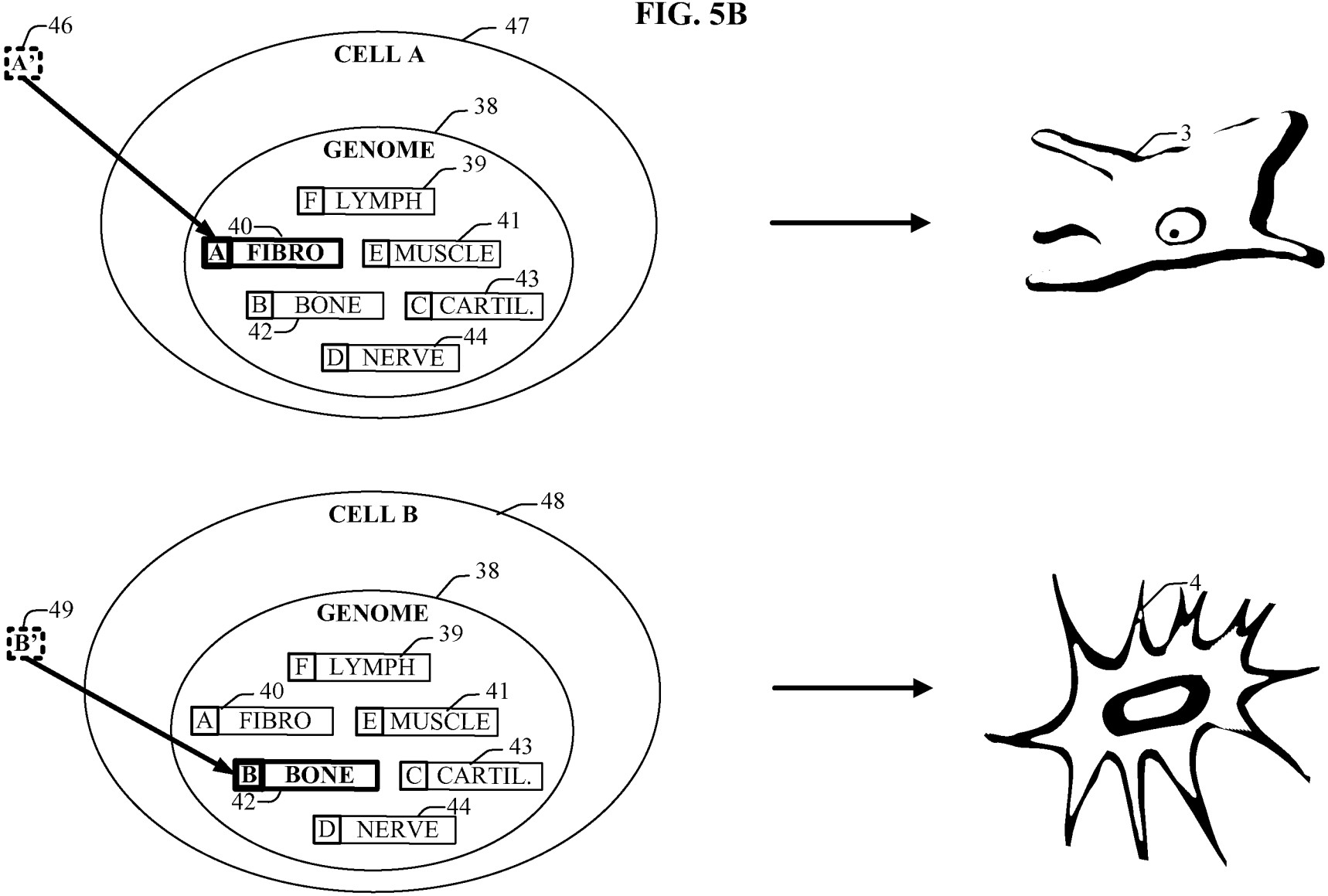

46
A'
47
CELL A
38
GENOME
39
F LYMPH
40
A FIBRO
41
E MUSCLE
43
B BONE
C CARTIL.
42
44
D NERVE
3
48
CELL B
49
B'
38
GENOME
39
F LYMPH
40
A FIBRO
41
E MUSCLE
43
B BONE
C CARTIL.
42
44
D NERVE
4

FIG. 6

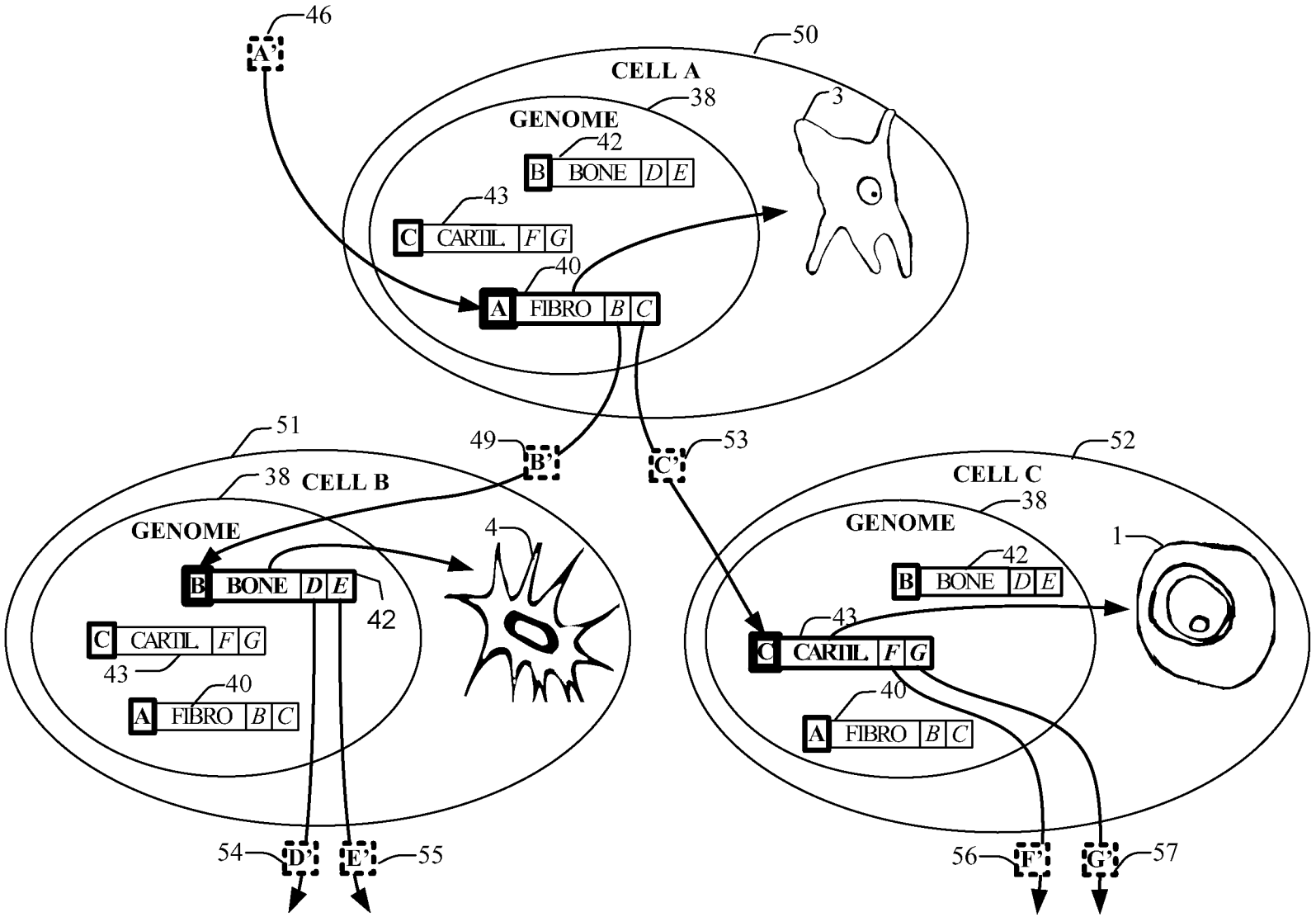

46
A'
50
CELL A
38
GENOME
3
42
B BONE D E
43
C CARTIL F G
40
A FIBRO B C
49
B'
C'
53
51
38 CELL B
GENOME
4
B BONE D E
42
C CARTIL F G
43
40
A FIBRO B C
52
CELL C
38
GENOME
1
42
B BONE D E
43
C CARTIL F G
40
A FIBRO B C
54
D'
E'
55
56
F'
G'
57

FIG. 7

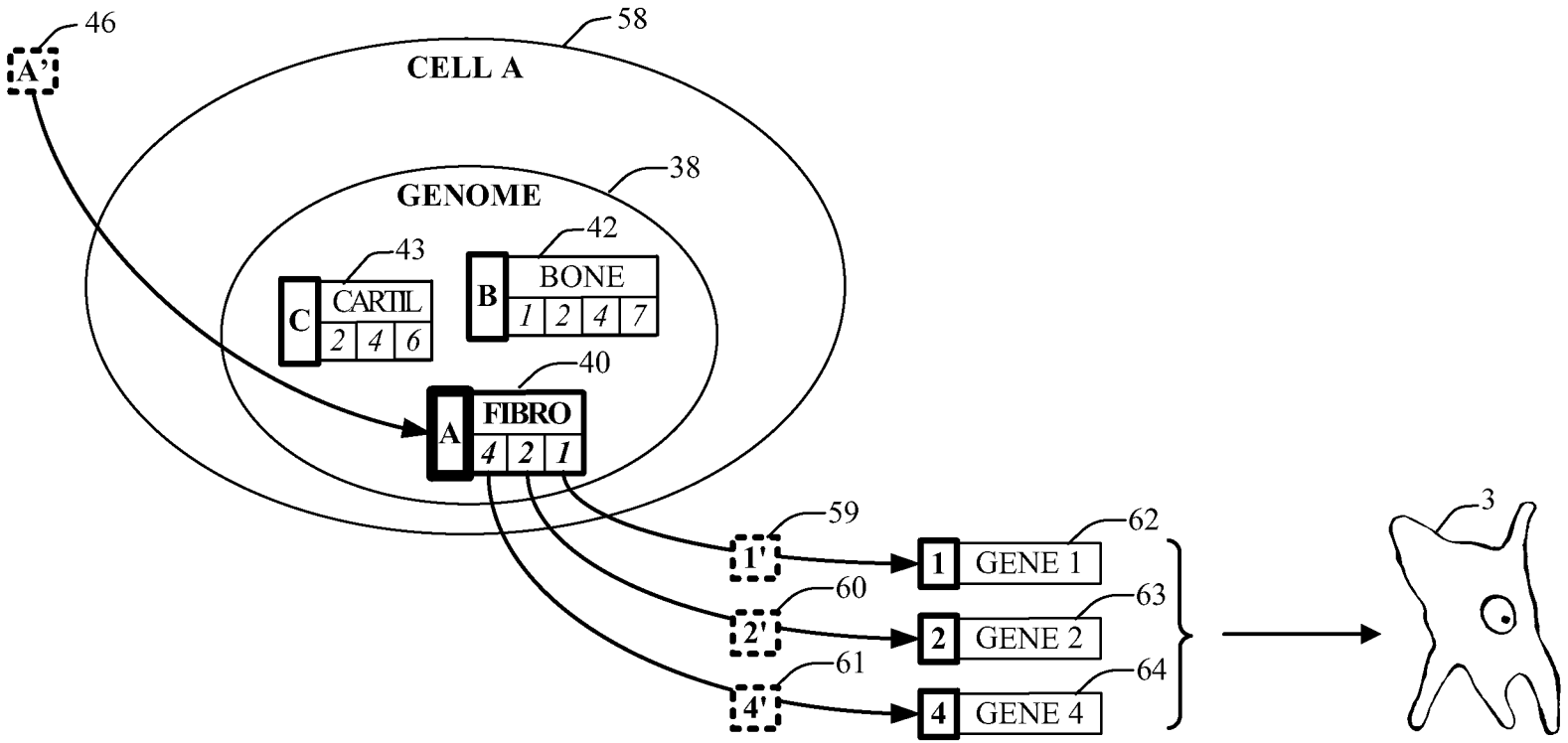

46
A'
58
CELL A
38
GENOME
43
C
CARTIL
2 4 6
42
B
BONE
1 2 4 7
40
A
FIBRO
4 2 1
59
1'
60
2'
61
4'
62
1
GENE 1
63
2
GENE 2
64
4
GENE 4
3

FIG. 8

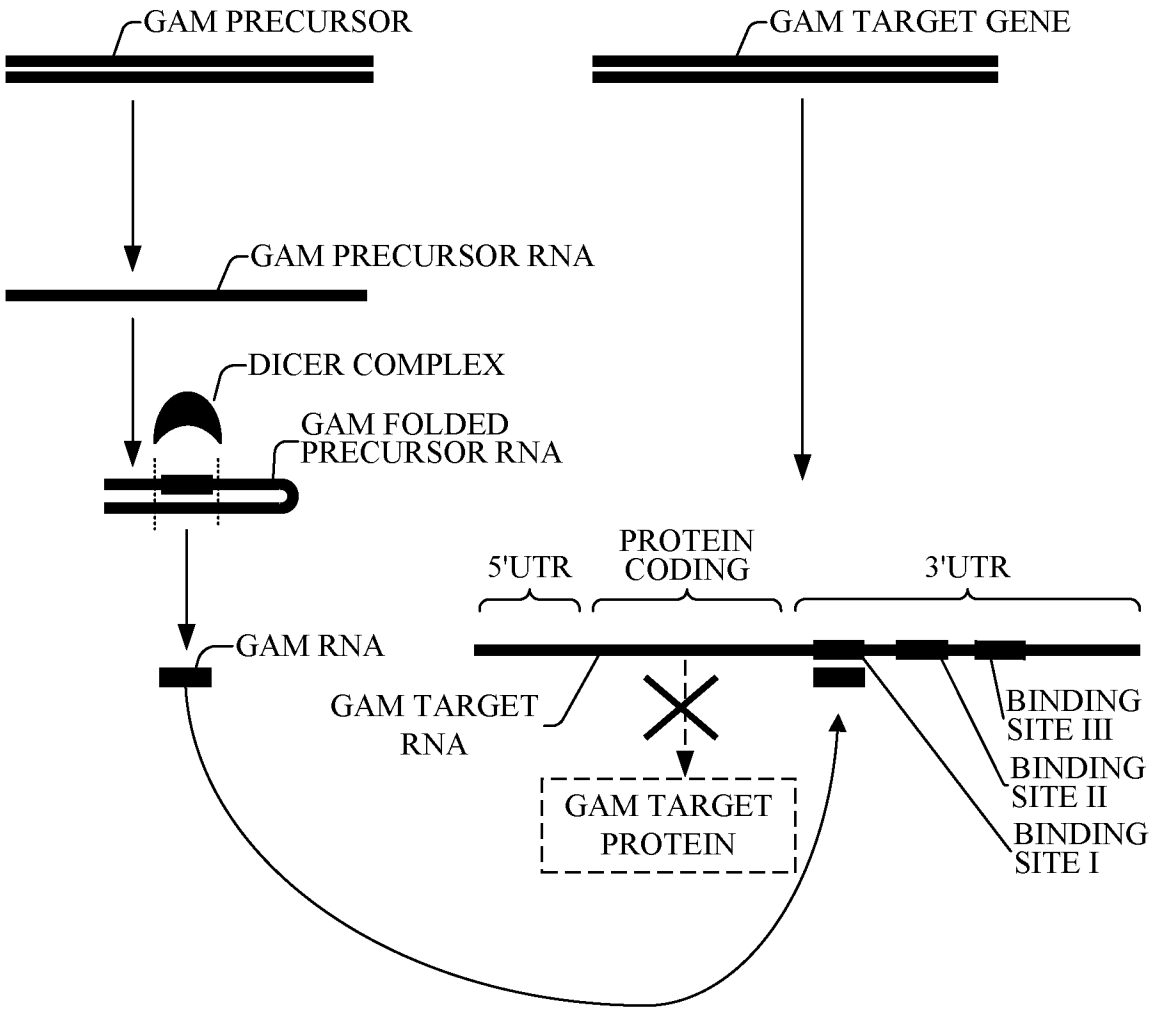

GAM PRECURSOR
GAM TARGET GENE
GAM PRECURSOR RNA
DICER COMPLEX
GAM FOLDED
PRECURSOR RNA
5'UTR
PROTEIN
CODING
3'UTR
GAM RNA
GAM TARGET
RNA
BINDING
SITE III
BINDING
SITE II
BINDING
SITE I
GAM TARGET
PROTEIN

FIG. 9

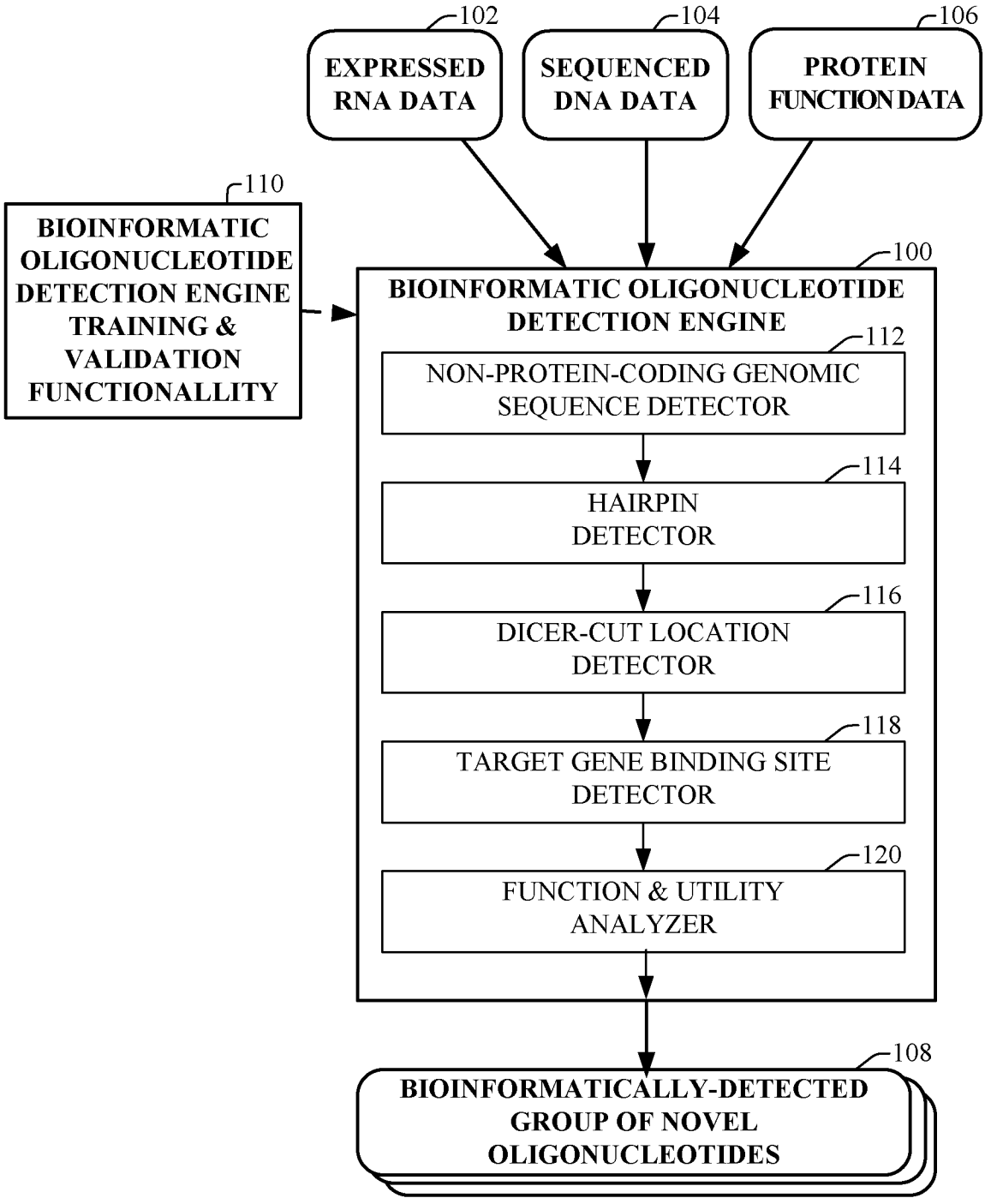

102
EXPRESSED RNA DATA
104
SEQUENCED DNA DATA
106
PROTEIN FUNCTION DATA
110
BIOINFORMATIC OLIGONUCLEOTIDE DETECTION ENGINE TRAINING & VALIDATION FUNCTIONALLITY
100
BIOINFORMATIC OLIGONUCLEOTIDE DETECTION ENGINE
112
NON-PROTEIN-CODING GENOMIC SEQUENCE DETECTOR
114
HAIRPIN DETECTOR
116
DICER-CUT LOCATION DETECTOR
118
TARGET GENE BINDING SITE DETECTOR
120
FUNCTION & UTILITY ANALYZER
108
BIOINFORMATICALLY-DETECTED GROUP OF NOVEL OLIGONUCLEOTIDES

FIG. 10

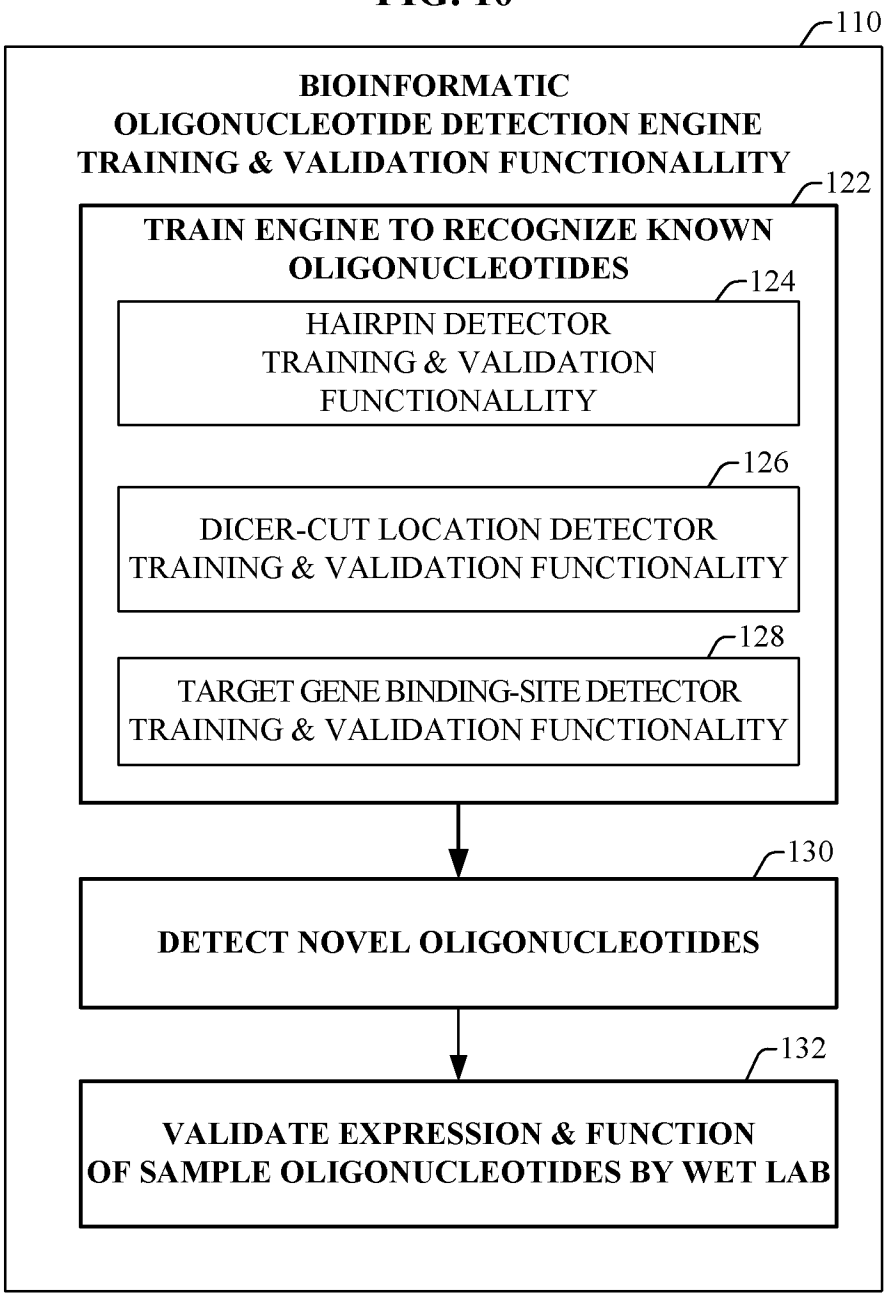

110
BIOINFORMATIC
OLIGONUCLEOTIDE DETECTION ENGINE
TRAINING & VALIDATION FUNCTIONALLITY
122
TRAIN ENGINE TO RECOGNIZE KNOWN
OLIGONUCLEOTIDES
124
HAIRPIN DETECTOR
TRAINING & VALIDATION
FUNCTIONALLITY
126
DICER-CUT LOCATION DETECTOR
TRAINING & VALIDATION FUNCTIONALITY
128
TARGET GENE BINDING-SITE DETECTOR
TRAINING & VALIDATION FUNCTIONALITY
130
DETECT NOVEL OLIGONUCLEOTIDES
132
VALIDATE EXPRESSION & FUNCTION
OF SAMPLE OLIGONUCLEOTIDES BY WET LAB

FIG. 11A

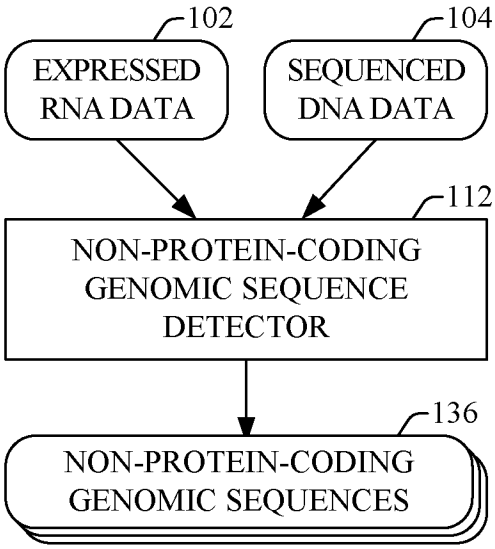


FIG. 11B

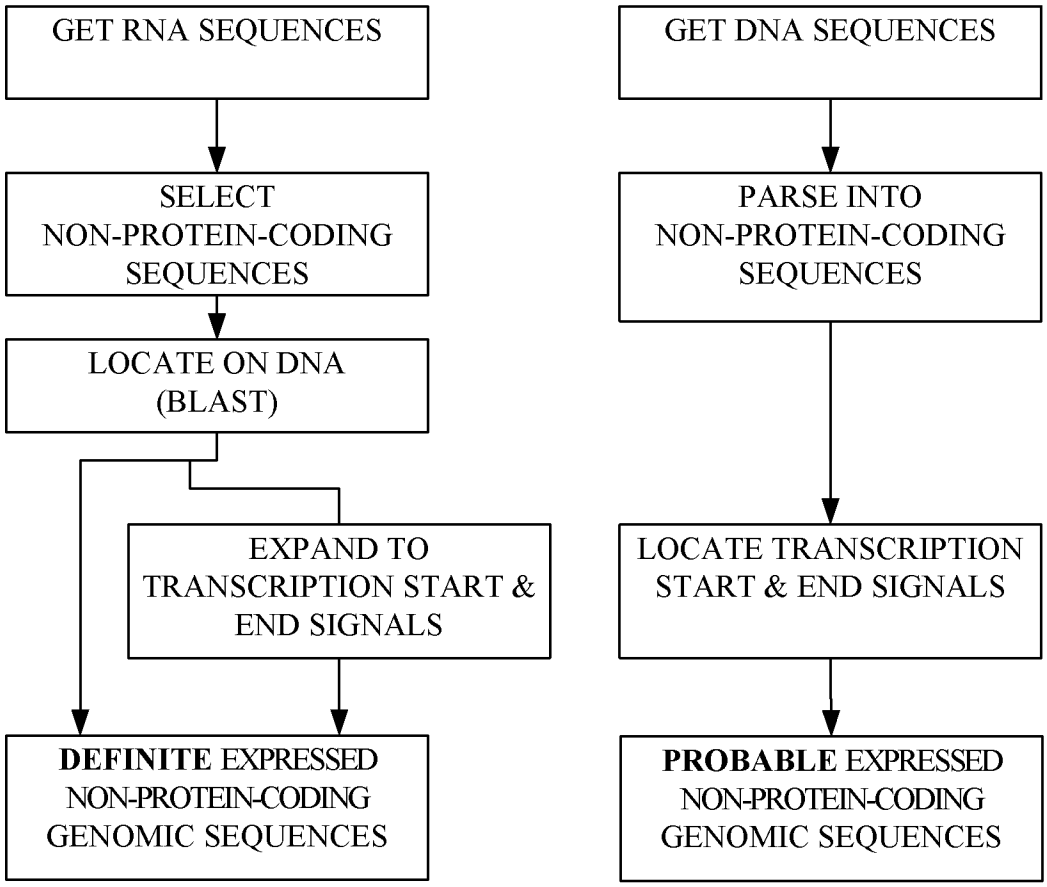


FIG. 12A

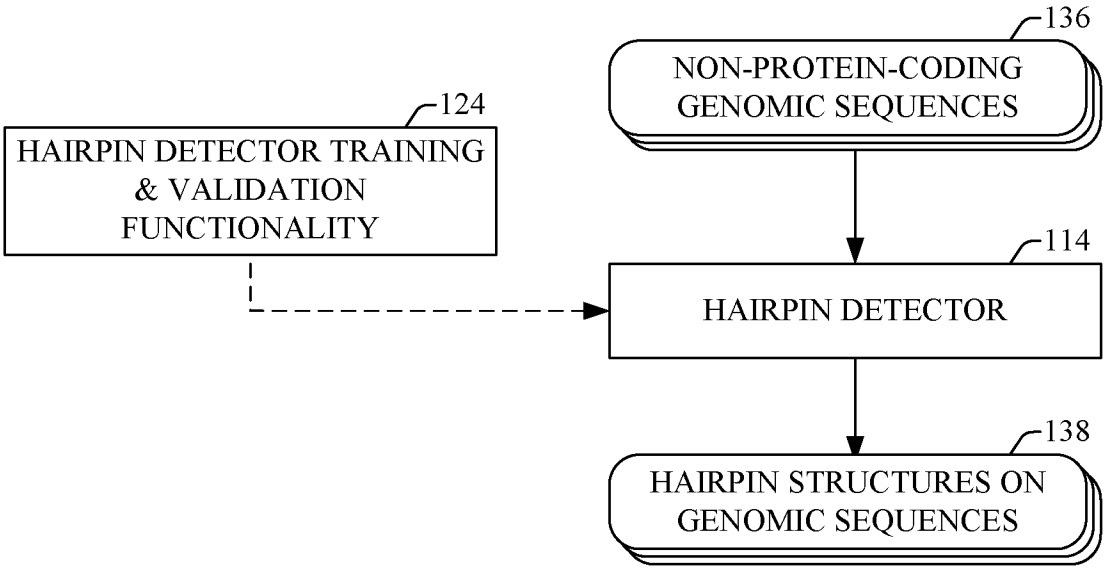


FIG. 12B

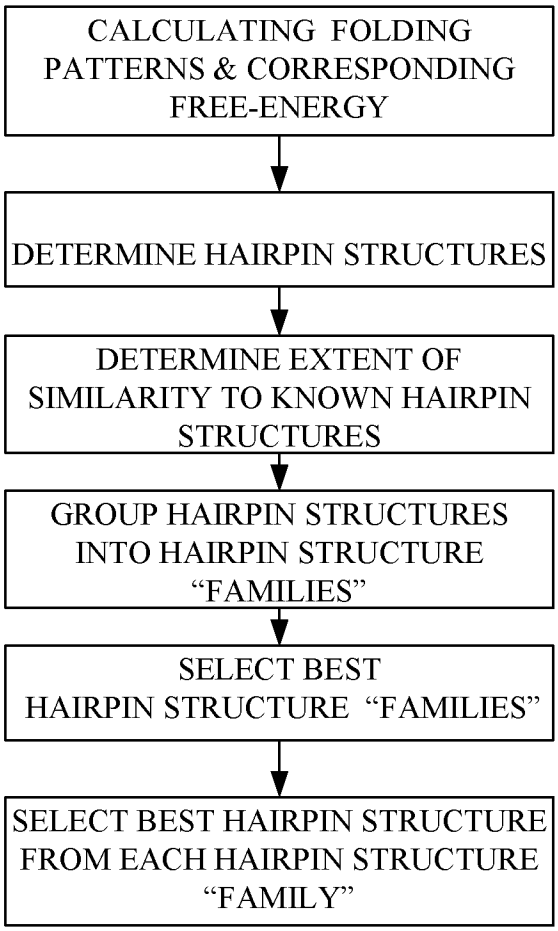


FIG. 13A

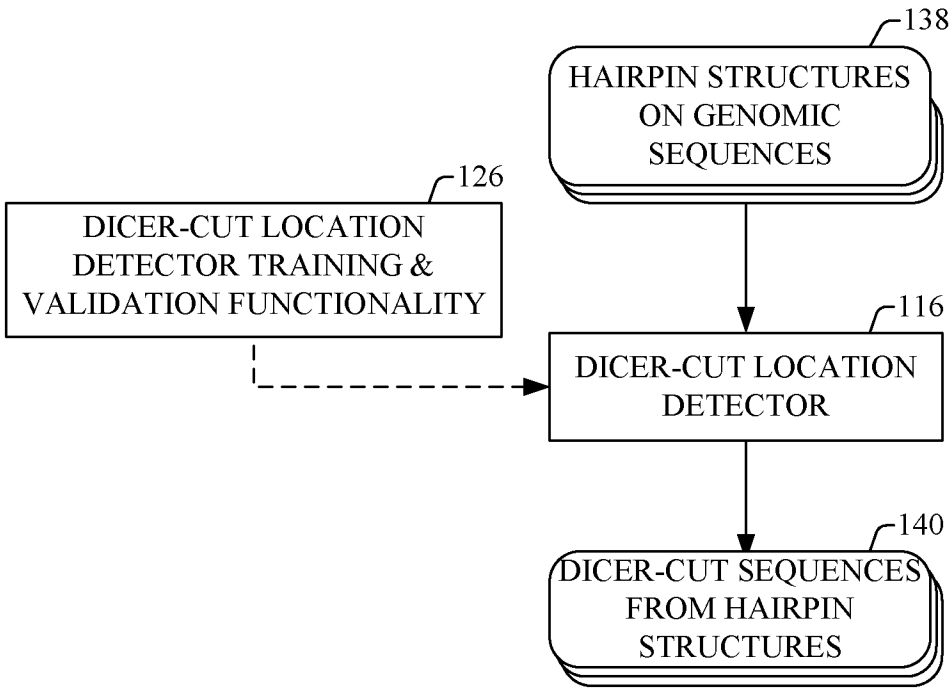

138
HAIRPIN STRUCTURES ON GENOMIC SEQUENCES
126
DICER-CUT LOCATION DETECTOR TRAINING & VALIDATION FUNCTIONALITY
116
DICER-CUT LOCATION DETECTOR
140
DICER-CUT SEQUENCES FROM HAIRPIN STRUCTURES

FIG. 13B

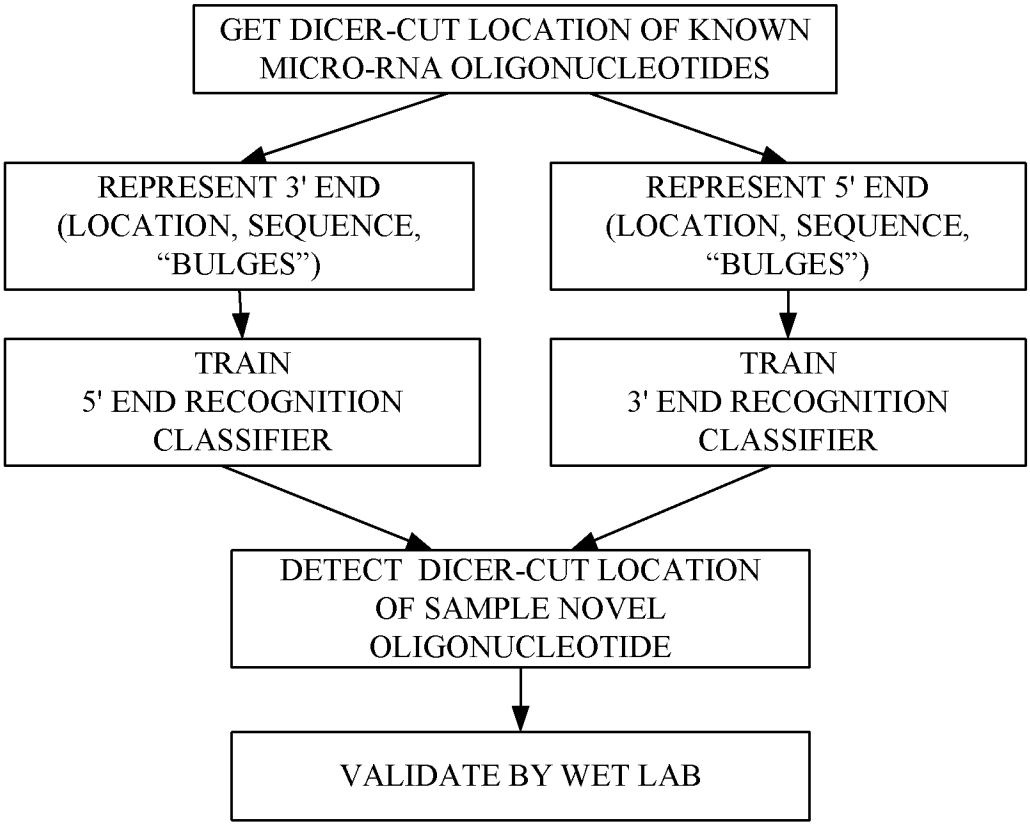

GET DICER-CUT LOCATION OF KNOWN MICRO-RNA OLIGONUCLEOTIDES
REPRESENT 3' END (LOCATION, SEQUENCE, "BULGES")
REPRESENT 5' END (LOCATION, SEQUENCE, "BULGES")
TRAIN 5' END RECOGNITION CLASSIFIER
TRAIN 3' END RECOGNITION CLASSIFIER
DETECT DICER-CUT LOCATION OF SAMPLE NOVEL OLIGONUCLEOTIDE
VALIDATE BY WET LAB

FIG. 13C

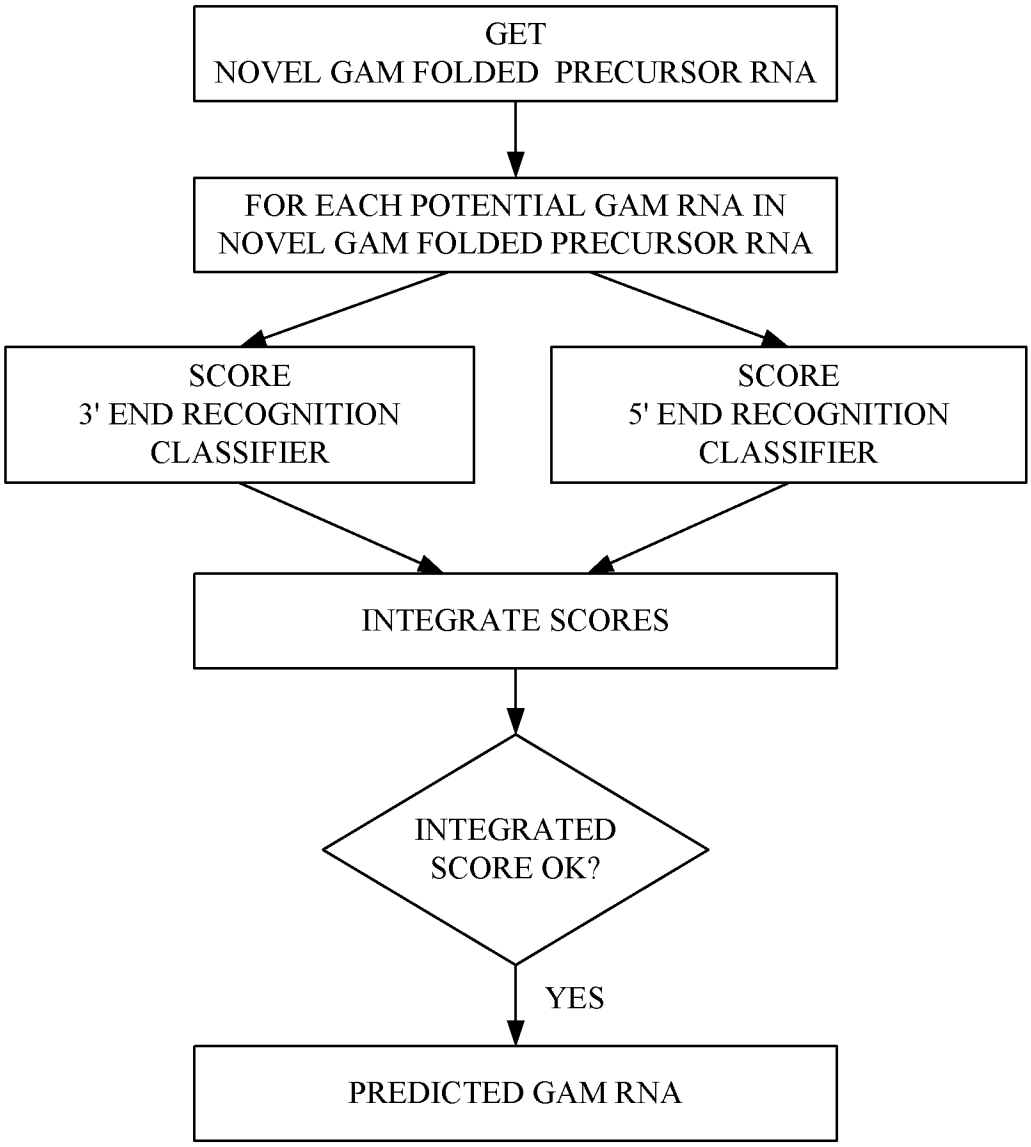

GET
NOVEL GAM FOLDED PRECURSOR RNA
FOR EACH POTENTIAL GAM RNA IN
NOVEL GAM FOLDED PRECURSOR RNA
SCORE
3' END RECOGNITION
CLASSIFIER
SCORE
5' END RECOGNITION
CLASSIFIER
INTEGRATE SCORES
INTEGRATED
SCORE OK?
YES
PREDICTED GAM RNA

FIG. 14A

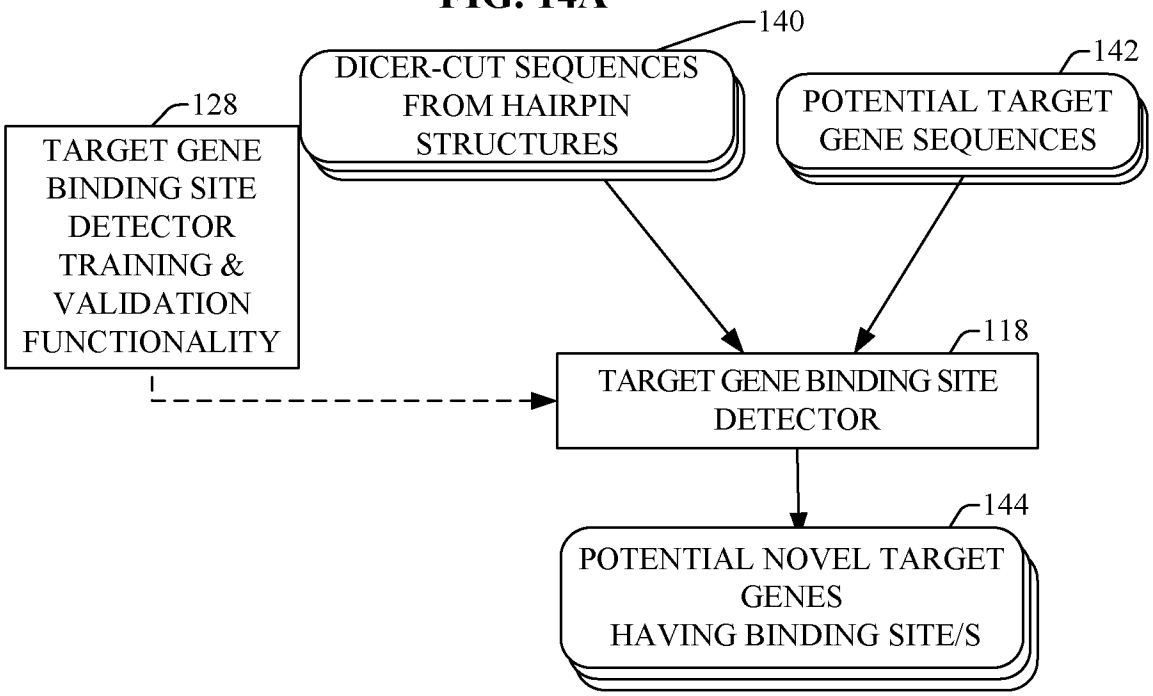


FIG. 14B

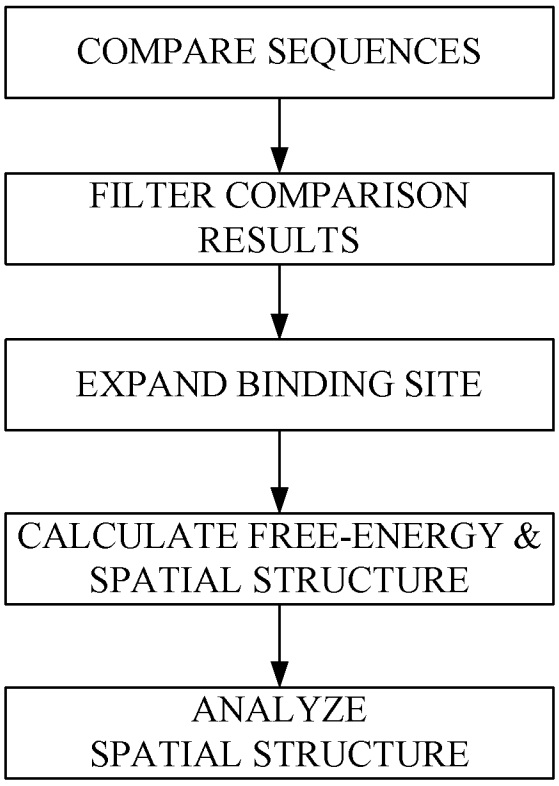


FIG. 15

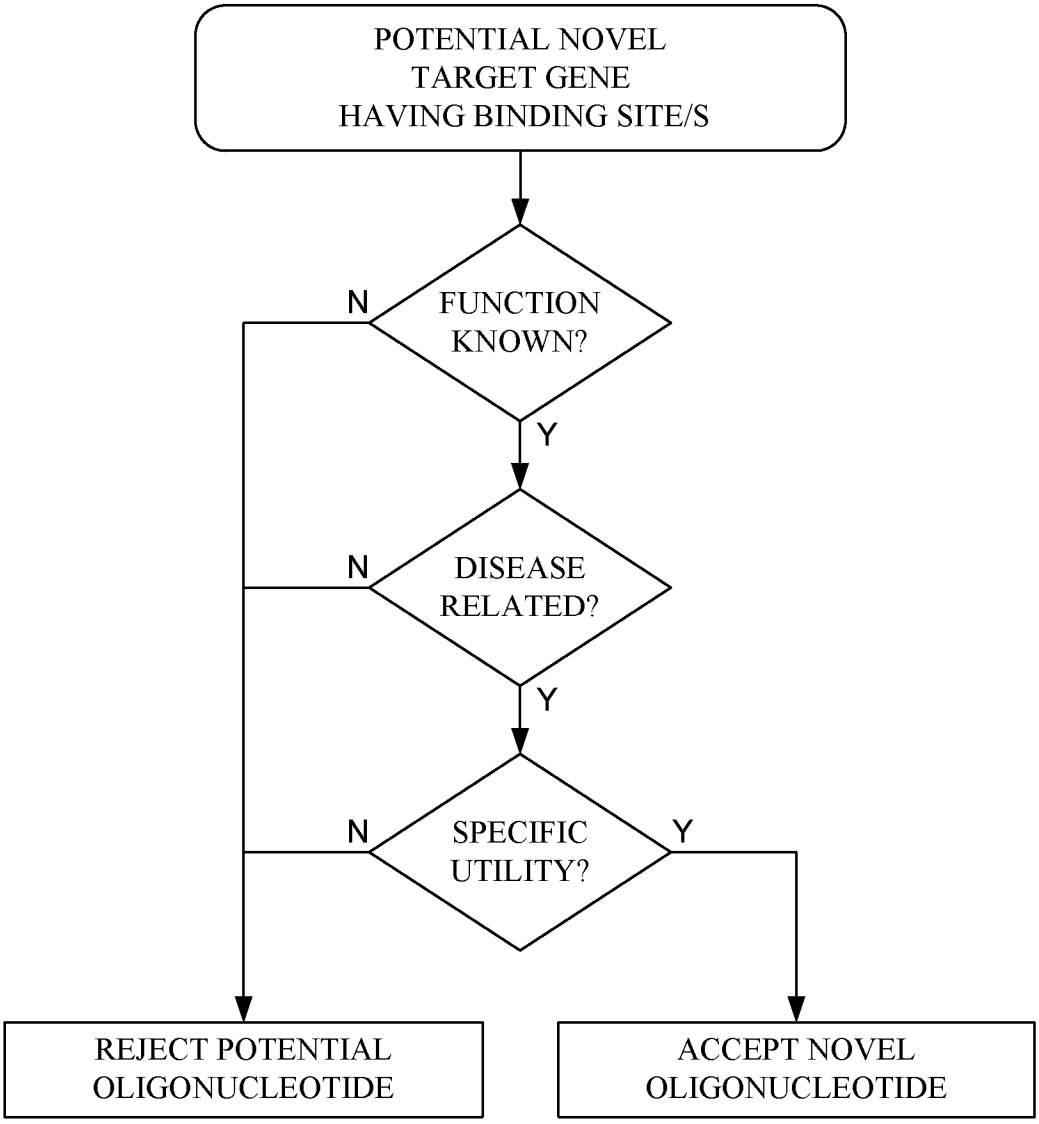

POTENTIAL NOVEL
TARGET GENE
HAVING BINDING SITE/S
FUNCTION
KNOWN?
N
Y
DISEASE
RELATED?
N
Y
SPECIFIC
UTILITY?
N
Y
REJECT POTENTIAL
OLIGONUCLEOTIDE
ACCEPT NOVEL
OLIGONUCLEOTIDE

FIG. 16

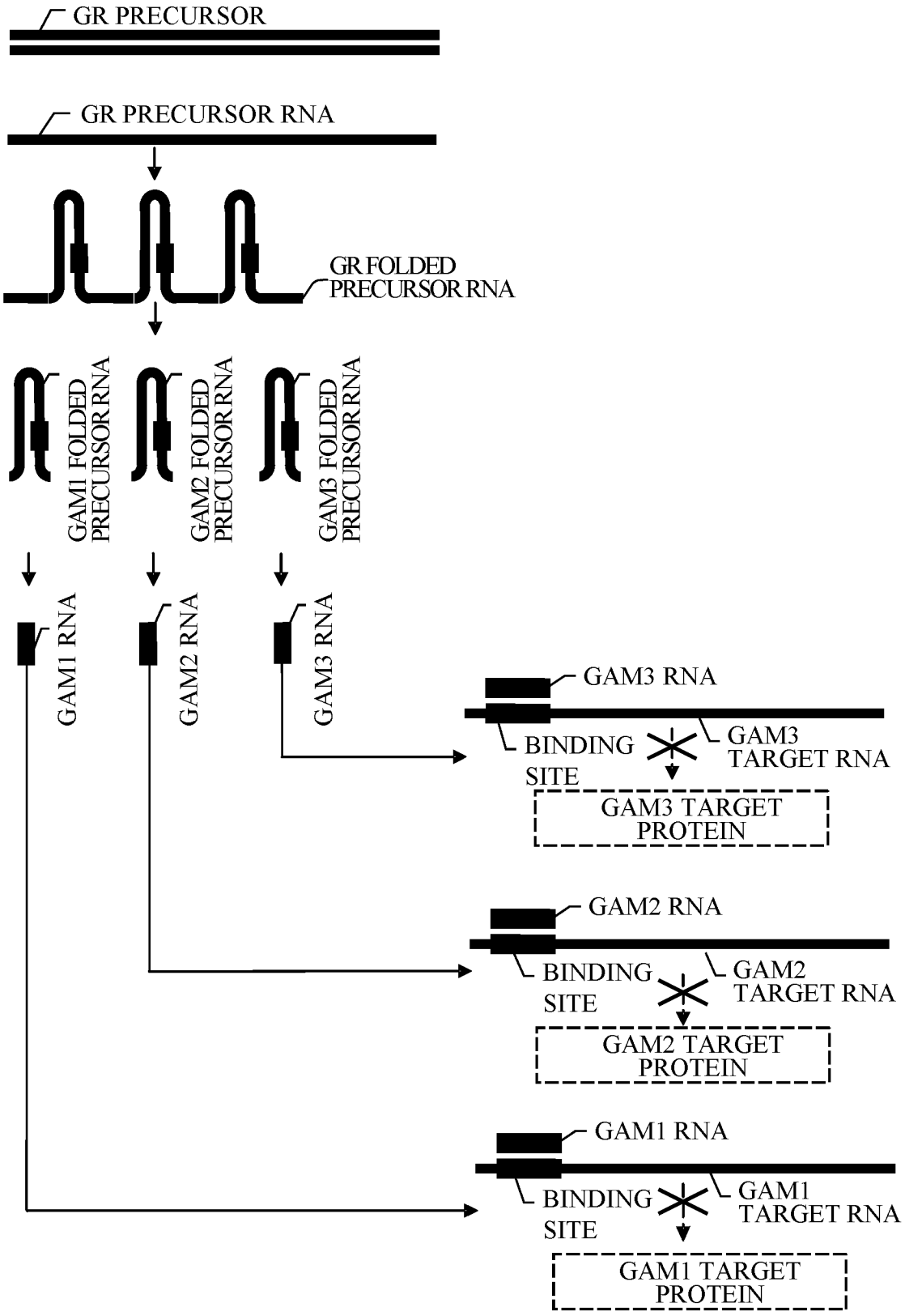

GR PRECURSOR
GR PRECURSOR RNA
GR FOLDED PRECURSOR RNA
GAM1 FOLDED PRECURSOR RNA
GAM2 FOLDED PRECURSOR RNA
GAM3 FOLDED PRECURSOR RNA
GAM1 RNA
GAM2 RNA
GAM3 RNA
GAM3 RNA
BINDING SITE
GAM3 TARGET RNA
GAM3 TARGET PROTEIN
GAM2 RNA
BINDING SITE
GAM2 TARGET RNA
GAM2 TARGET PROTEIN
GAM1 RNA
BINDING SITE
GAM1 TARGET RNA
GAM1 TARGET PROTEIN

FIG. 17

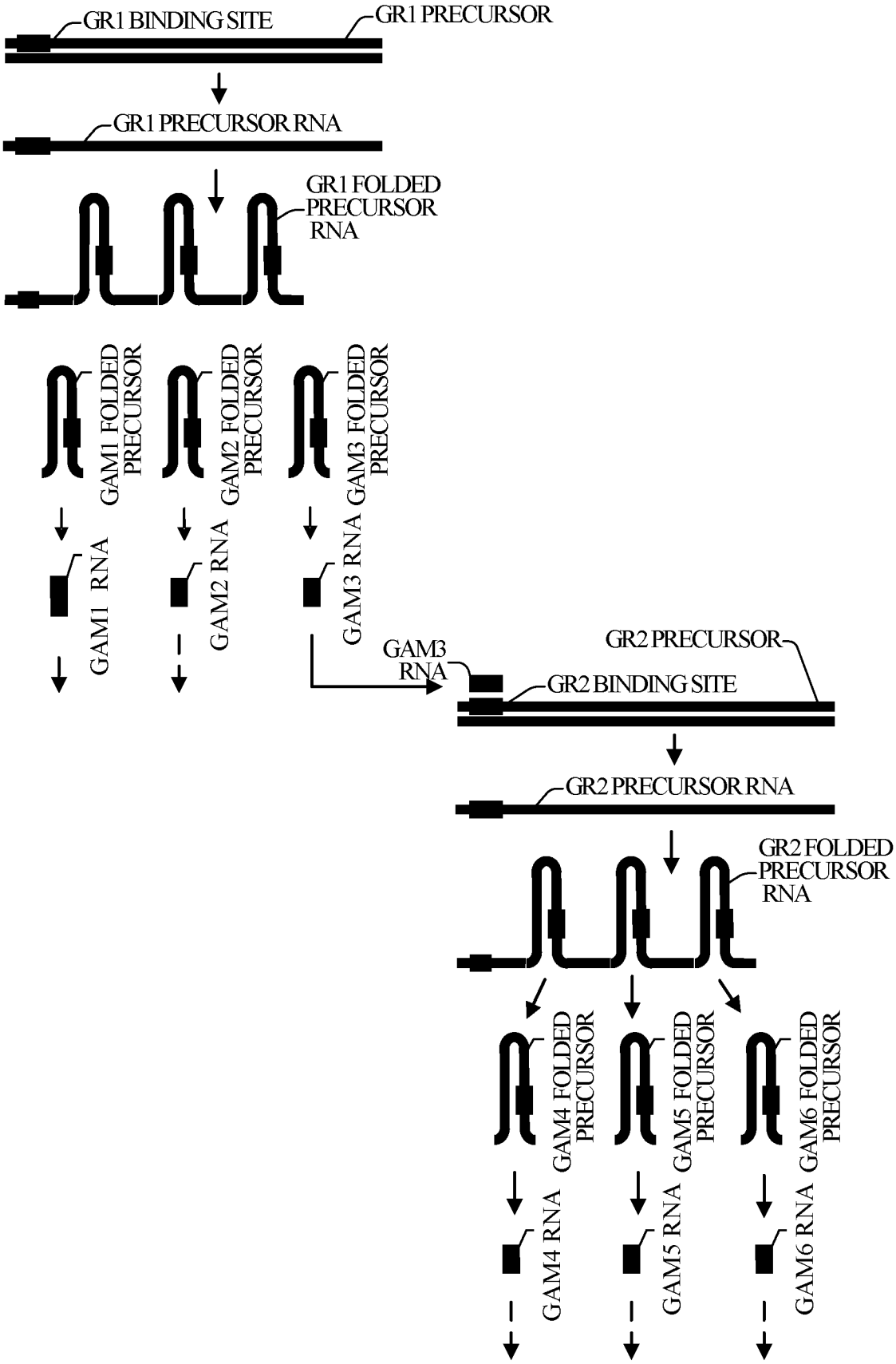

GR1 BINDING SITE
GR1 PRECURSOR
GR1 PRECURSOR RNA
GR1 FOLDED PRECURSOR RNA
GAM1 FOLDED PRECURSOR
GAM2 FOLDED PRECURSOR
GAM3 FOLDED PRECURSOR
GAM1 RNA
GAM2 RNA
GAM3 RNA
GAM3 RNA
GR2 PRECURSOR
GR2 BINDING SITE
GR2 PRECURSOR RNA
GR2 FOLDED PRECURSOR RNA
GAM4 FOLDED PRECURSOR
GAM5 FOLDED PRECURSOR
GAM6 FOLDED PRECURSOR
GAM4 RNA
GAM5 RNA
GAM6 RNA

FIG. 18

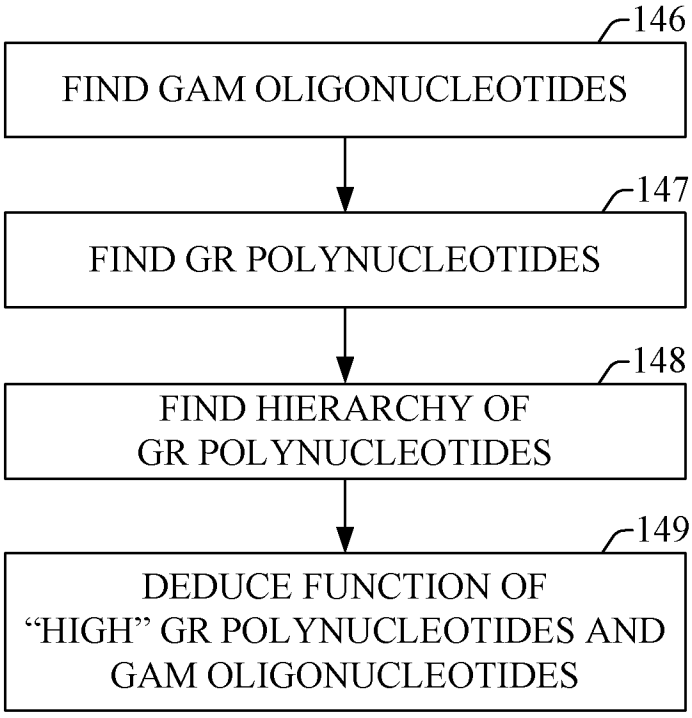

146
FIND GAM OLIGONUCLEOTIDES
147
FIND GR POLYNUCLEOTIDES
148
FIND HIERARCHY OF
GR POLYNUCLEOTIDES
149
DEDUCE FUNCTION OF
"HIGH" GR POLYNUCLEOTIDES AND
GAM OLIGONUCLEOTIDES

FIG. 19

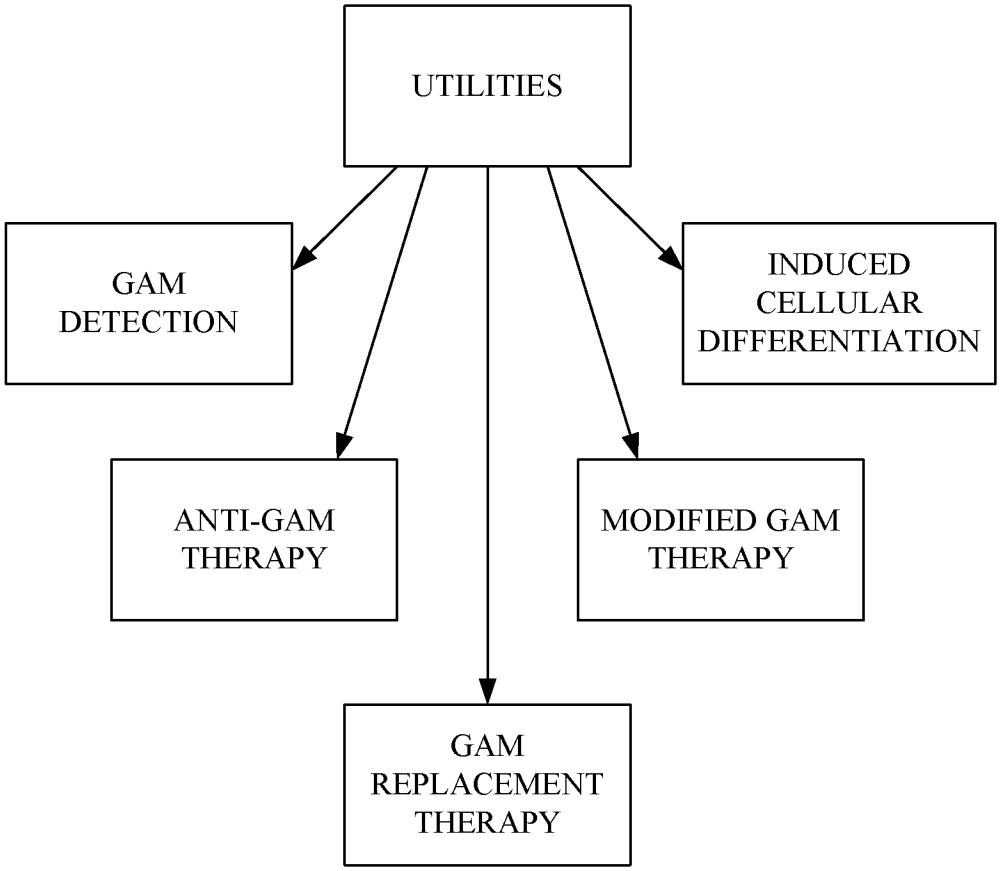

UTILITIES
GAM DETECTION
INDUCED CELLULAR DIFFERENTIATION
ANTI-GAM THERAPY
MODIFIED GAM THERAPY
GAM REPLACEMENT THERAPY

FIG. 20A

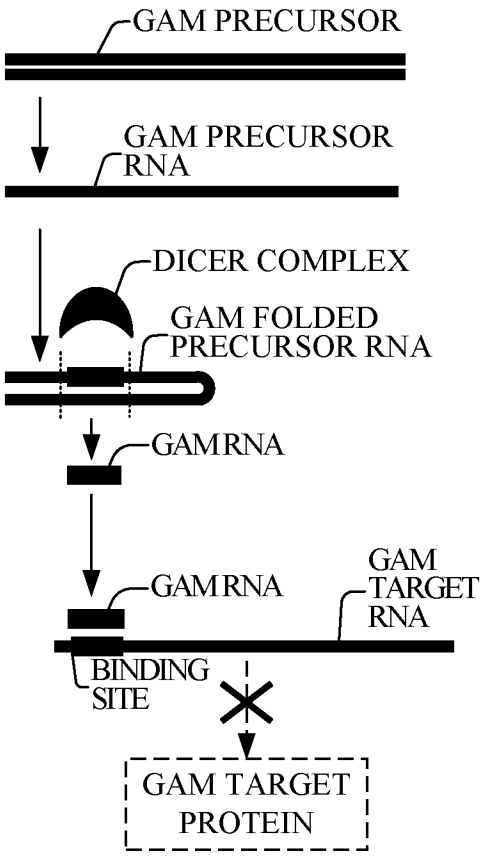


FIG. 20B

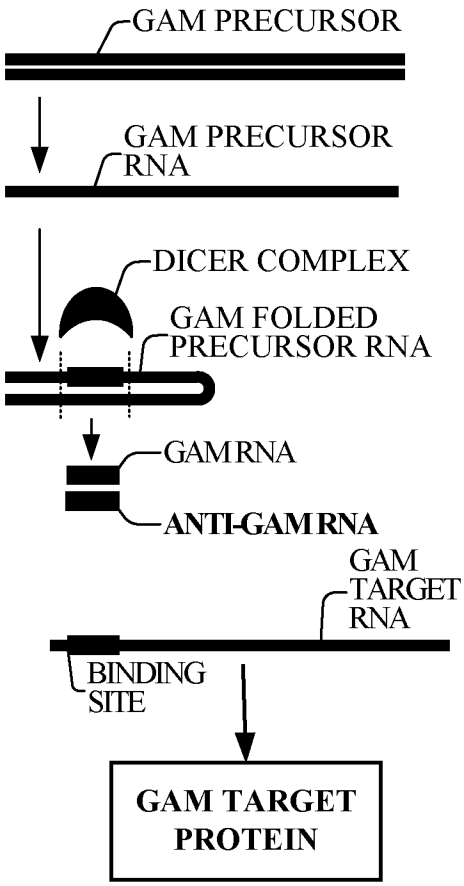


FIG. 21A

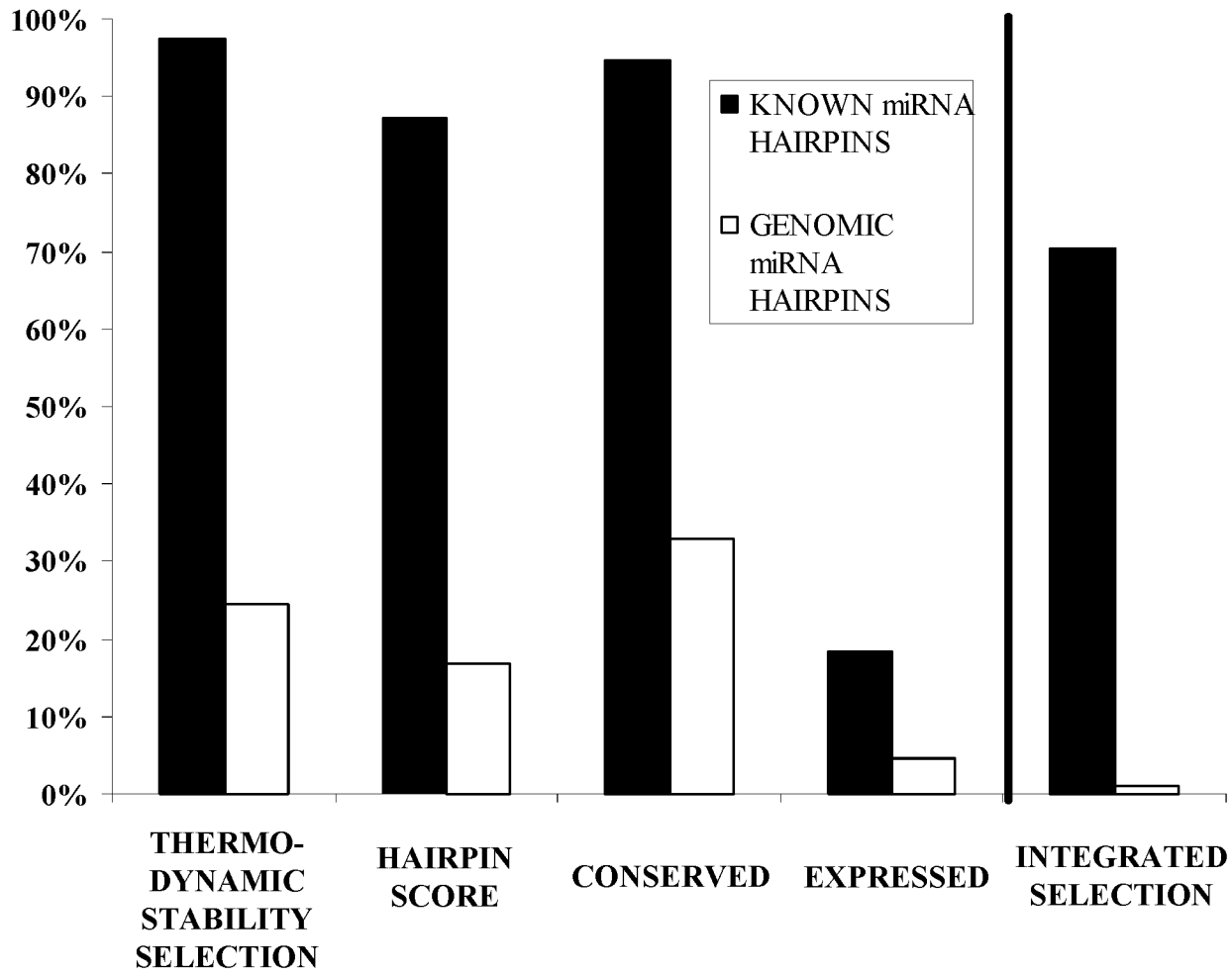

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
KNOWN miRNA HAIRPINS
GENOMIC miRNA HAIRPINS
THERMO-DYNAMIC STABILITY SELECTION
HAIRPIN SCORE
CONSERVED
EXPRESSED
INTEGRATED SELECTION

FIG. 21B

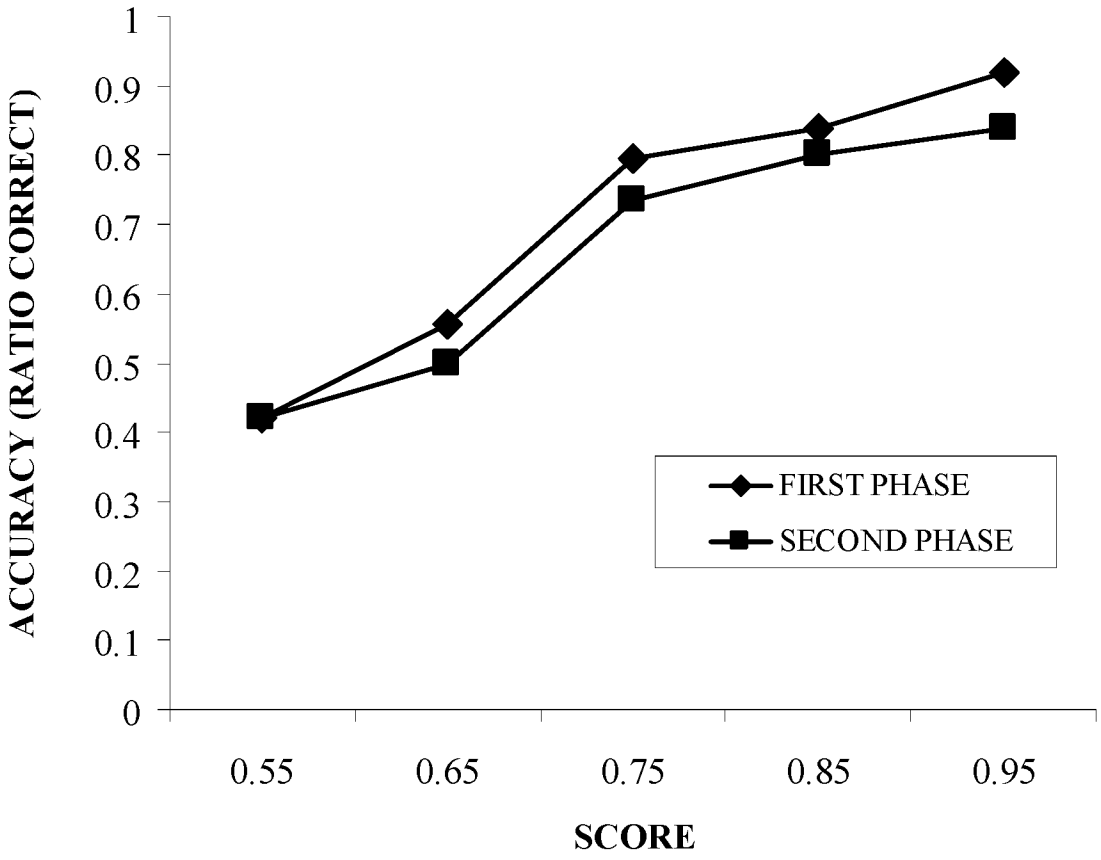

ACCURACY (RATIO CORRECT)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.55
0.65
0.75
0.85
0.95
SCORE
FIRST PHASE
SECOND PHASE

FIG. 21C

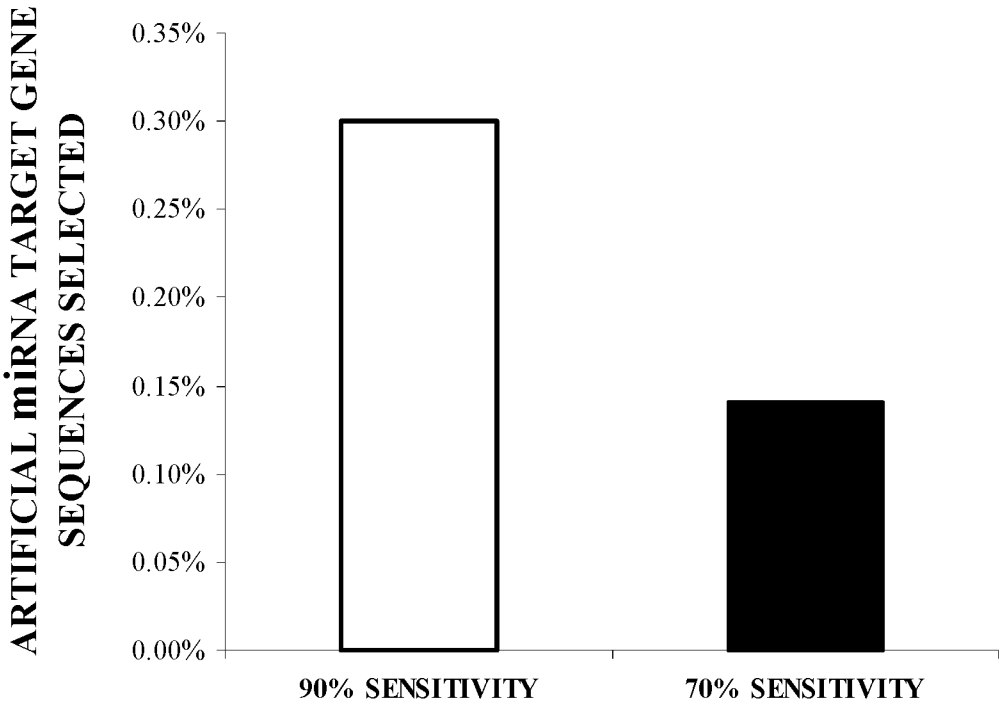

ARTIFICIAL miRNA TARGET GENE SEQUENCES SELECTED
0.35%
0.30%
0.25%
0.20%
0.15%
0.10%
0.05%
0.00%
90% SENSITIVITY
70% SENSITIVITY

FIG. 22

ROW	PRIMER SEQUENCE	SEQUENCED SEQUENCE	PREDICTED GAM RNA	DIST-ANCE	GAM NAME
1*	AATTGCTTGAAC	CCAGGAAGTGGA	AATTGCTTGAACCCAGGAAGTGGA	0	25-A
2*	ACTGCACTCC	AGCCTGGGC	ACTGCACTCCAGCCTGGGCTAC	0	351661-A
3	CACTGCACTC	CAGCCCGAGCAACA	CACTGCACTCCAGCCCGAGCAA	0	351946-A
4	CTAGACTGAAG	CTCCTTGAGGAC	CTAGACTGAAGCTCCTTGAGGA	0	352759-A
5	GAAGTTTGAAG	CCTGTTGTTCA	GAAGTTTGAAGCCTGTTGTTCA	0	4426-A
6	TCACTGCAAC	CTCCACCA	(TCACTGCAACCTCCACCACGTG),(TCACTGCAACCTCCACCAGCCT)	0	(357950-A),(352721-A)
7*	TCTAAGAGAAAG	GAAGTTCAGA	TCTAAGAGAAAGGAAGTTCAGA	0	337950-A
8	GGGCAGTGGA	GCTGGAA	GGGCGTGGAGCTGGAATGATGT	1	351996-A
9	AATTGCTTGAAC	CCAAGAAGTGGA	AATCACTTGAACCCAAGAAGTG	2	351874-A
10	AGCAGCCCA	GGGTTTTGT	AGCAAGACCAGGGTTTTGTGTT	2	352083-A
11	AGGCAAGACG	GACCAGA	AGGCAGAGAGGACCAGAGACT	2	351944-A
12	AGGGAAAGAAT	TAATGTGAA	GGGAAATAATTAATGTGAAGTC	2	353325-A
13	AGGGAAAGAAT	TAATGTGAG	AGGAAAAAAATTAATGTGAGTC	2	352649-A
14	ATTCAGTTG	CCCATGTTT	(ATTGTTGCCCATGTTTTTATTT),(TATTCATTGCCCATGTTTGTGA)	2	A),(352957-A,352960-A)
15	CTAGACTGAAG	CTCCTTGAGG	CTGGACTGAGCTCCTTGAGGCC	2	352288-A
16	TTCAGAGTGGT	TAAGTTCTG	TTCTGATGGTTAAGTTCTGTCA	2	353875-A
17	TTCAGAGTGGT	TAAGTTCTGC	TTCAAGTGTTTAAGTTCTGCTT	2	351940-A
18	AGCAGCCCA	GAAGGAAGC	AGGCCAAGAAGGAAGCAGAGG	3	352496-A
19	AGTTTGCCTTG	TAAGAAAAG	AGTTTGTGTAAGAAAAGC	3	352518-A
20	ATCAGAGGGTG	GGTGCTAA	ATTAGGAGAGTGGGTGCTAAGT	3	352511-A
21	ATGGTGGGAG	AGTTTGTCAGT	TGGAGGAGAGTTTGTCAGTATAG	3	353484-A
22	CCCAGGAAG	TGGAGCCTGGGC	CCCGGGTGGAGCCTGGGCTGTG	3	351990-A
23	GGGCAGTGGA	GGTCCGT	AGGGCAGGAGGTCCGTCCCTTC	3	353880-A
24	GGGCAGTGGA	TCTAGAC	GTGACAGTGAATCTAGACAGAC	3	352810-A
25	TCAAGCTCATTC	CACTAAA	CTCAGCTCATCCACTAAATCCC	3	353184-A
26	TGGAAAGTT	GGTTGTATGGTT	GGAATGGTGGTTGTATGGTTG	3	353855-A
27	TGGAGAGTT	CCATATTTTG	TGATAGATCCATATTTTGGTAA	3	352004-A
28	TGGAGAGTT	GTTTGTACAGT	TGGGTTTTGTTTGTACAGTGTA	3	353160-A
29	TCACTGCAAC	CTCCACC	TCACTGCAACCTCCACCTTCCG	0	353856-A

FIG. 23A

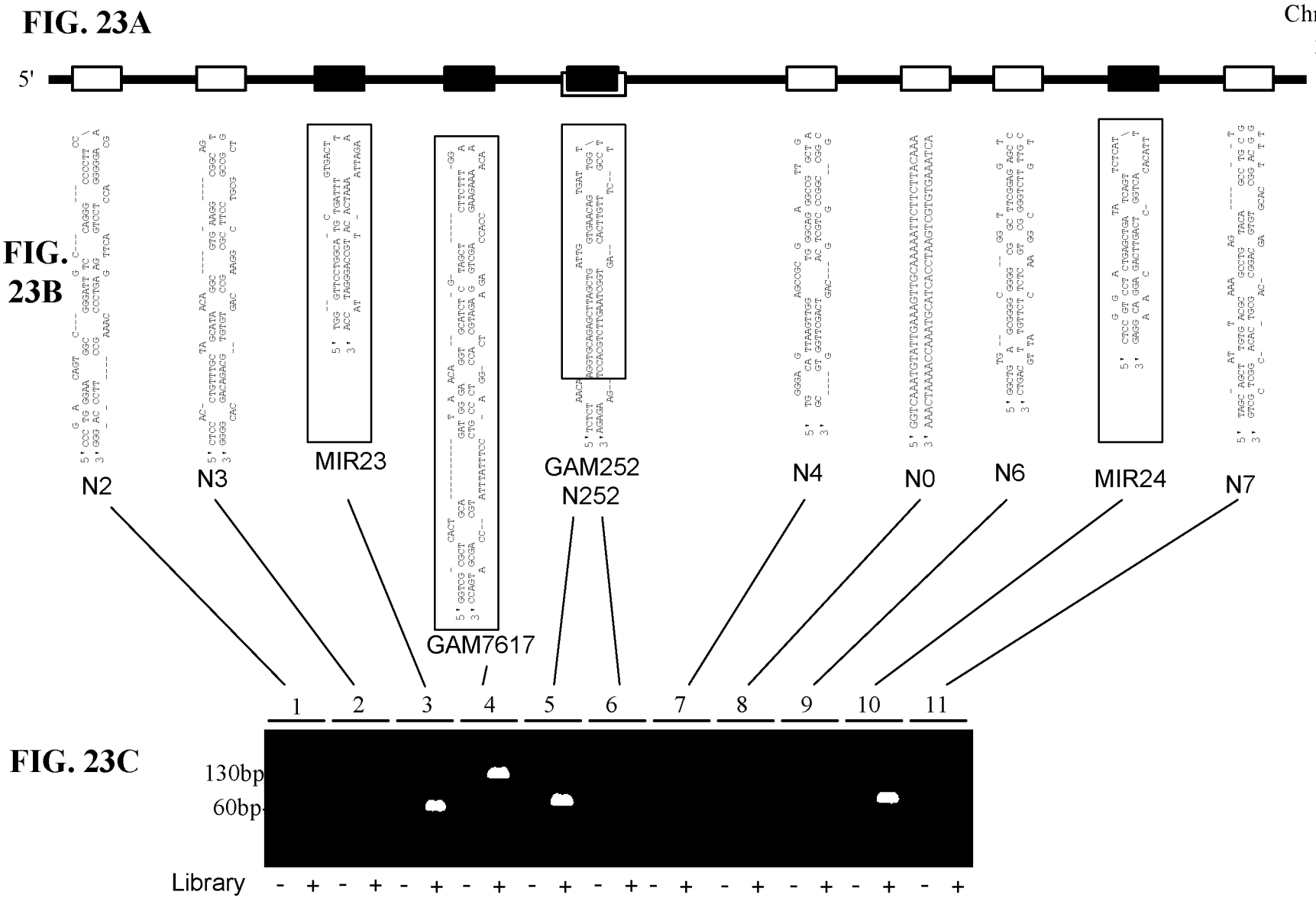
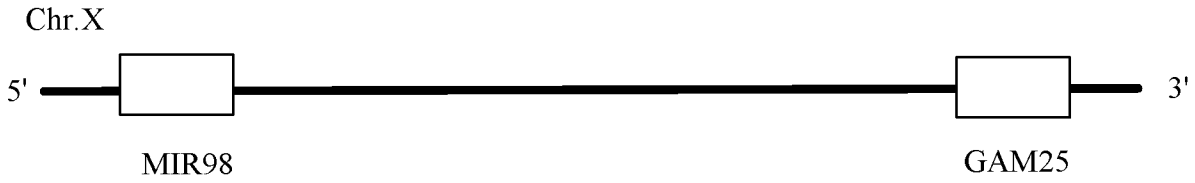


FIG. 23B

FIG. 23C

FIG. 24A

EST72223 (705 nt.)



EST72223 sequence:

CCCTTATTAGAGGATTCTGCTCATGCCAGGGTGAGGTAGTAAGTTGTATTG
TTGTGGGGTAGGGATATTAGGCCCCAATTAGAAGATAACTATACAACT **MIR98**
TACTACTTTCCCTGGTGTGTGGCATATTCACACTTAGTCTTAGCAGTGTTGCC
TCCATCAGACAAAGTTGTAGATGTTCCTTGGATAATTTGGACTGGAAGAAAAGA
GACATGGAAGGGGACAGATGGTGTTTAGGGTGAGGCAGATGTCATTATAAAGT
GACTTGTCTTTCATTAATTGGAGCATATAATTATTTTACCTTTGGGCATGAACTC
ATTTTGCTATTCTTCAACTGTGTAATGATTGCATTTTATTAGTAATAGAACAGGA
ATGTGTGCAAGGGAATGGAAAGCATACTTTAAGAATTTTGGGCCAGGCGCGGT
GGTTCATGCCTGTAATCCCAGCATTTTTGGGAGGCCGAGGCGGGTGGATCAC
CTGAGGTCAGGAGTTCGAGACCAACCTGGCCAACACGGCGAAACCCCGCCTC
TACTCAAATACAAAAATTAGCCAGGCTTGGTGACACTCGCCTGTGGTCCCAGC
TACTCAGGAGGCTGAGGCAGGAGAATTGCTTGAACCCAGGAAGTGGAG **GAM25**
GCTTCAGTGAGCTGAGAACACGCCACTGCACTCCAGTCCTGGGCAAC
AGAGCAAGACTCTGTCTCAGGAAAAAAAAAG

FIG. 24B

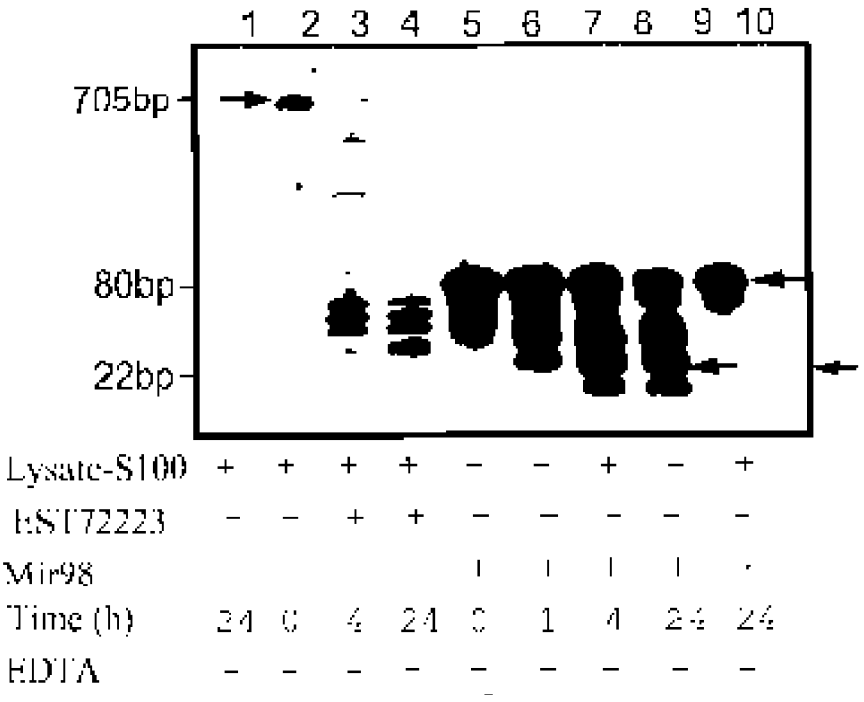
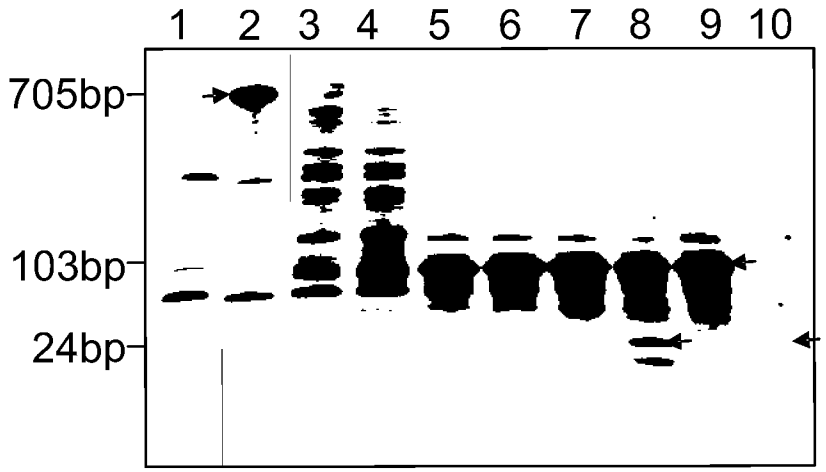
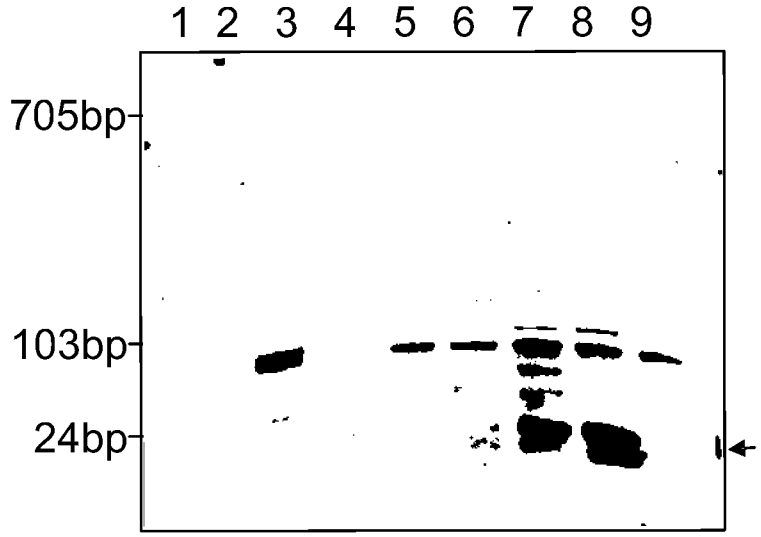


FIG. 24C



Lysate-S100	+	+	+	+	+	+	+	+	+
EST72223	–	+	+	+	–	–	–	–	–
GAM25	–	–	–	–	+	+	+	+	+
Time (h)	24	0	4	24	0	0.5	1	24	24
EDTA	–	–	–	–	–	–	–	–	+

FIG. 24D



Lysate-S100	+	+	+	+	+	+	+	+	+
EST72223	–	+	+	+	–	–	–	–	–
GAM25	–	–	–	–	+	+	+	+	+
Time (h)	24	0	4	24	0	0.5	1	24	24
EDTA	–	–	–	–	–	–	–	–	+

FIG. 25A

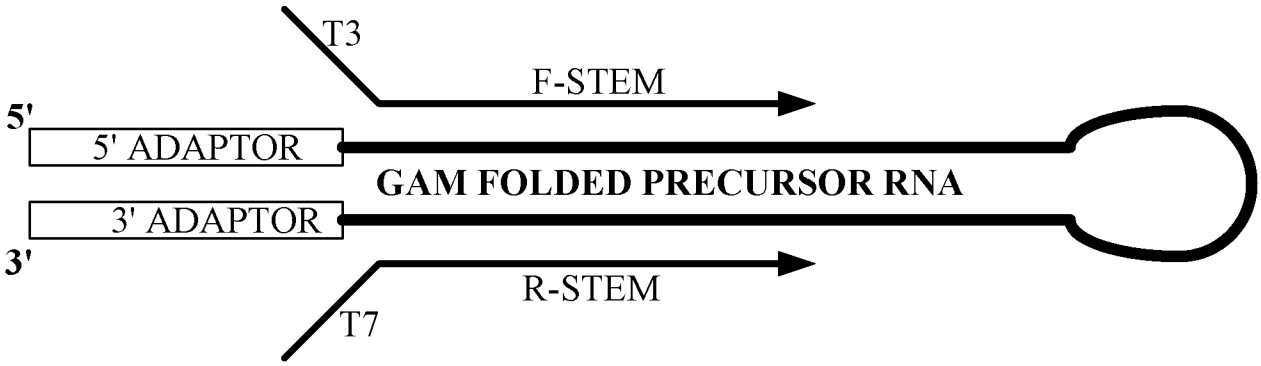


FIG. 25B

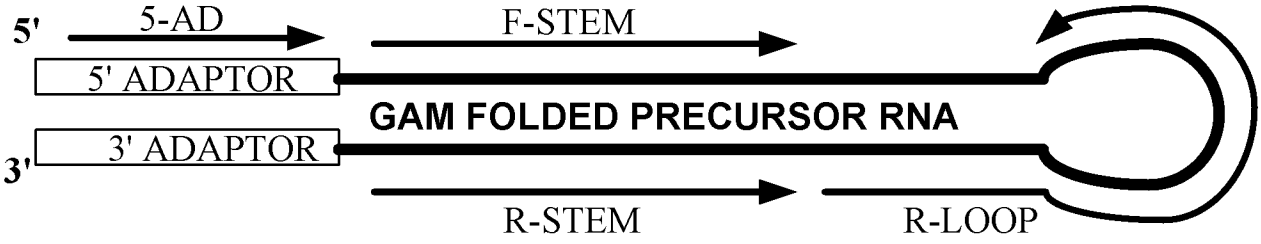


FIG. 25C

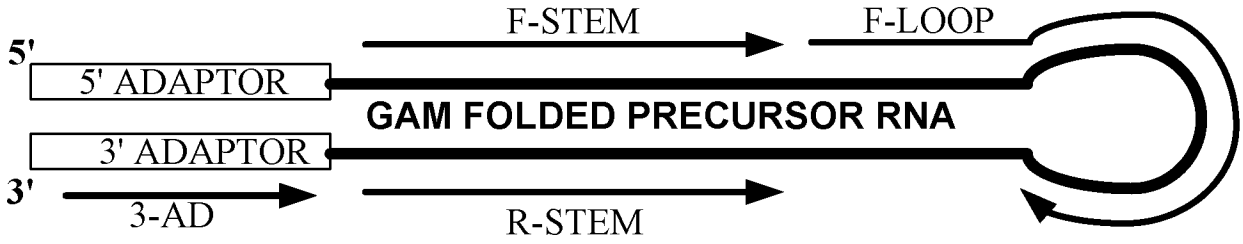


FIG. 25D

PRE #	PREDICTED PRECURSOR SEQUENCE	PRIMER1 TYPE/NAME	PRIMER1 SEQUENCE	PRIMER2 TYPE/NAME	PRIMER2 SEQUENCE	METHOD	OBSERVED SEQUENCE	GAM NAME
1	AATGCTGAGTCCTGTGAGTCTTCCTAGCAAATCAAATCTGGAAGGGGTCTTGAGGACTCCAGCATT	F_STEM_1_3	GAGTCCTGTGAGTCTTCCTAGC	R_STEM_1_3	TGCTGGAGTCCTCAAGACC	A		
2	TGAGCCCTCAGCCCTCATGGCTTTCCCGATGCTCACCGGTGCAGAGGAGCCAGCTGGGGAGCCTCTGT	R_LOOP_2_1	AAAGCCATGAGGGCTGAGG	R_STEM_2_1	GTGAGCATCGGGAAAGCCA	B		
3	ACTGTTGGTCTTCTGTTTAGCCATTATTCTCAGTTCTGTGCAGGAGTGAGCTGAAACAAAGTTGTATAGCCCAGAGAGTGAGAAGCTGCATTTCATGTCTCCCAACAGT	F_STEM_3_3	TTCTCAGTTCTGTGCAGGAGTG	R_STEM_3_3	CTTCTCACTCTCTGGGCTATAC	A		

FIG. 26A

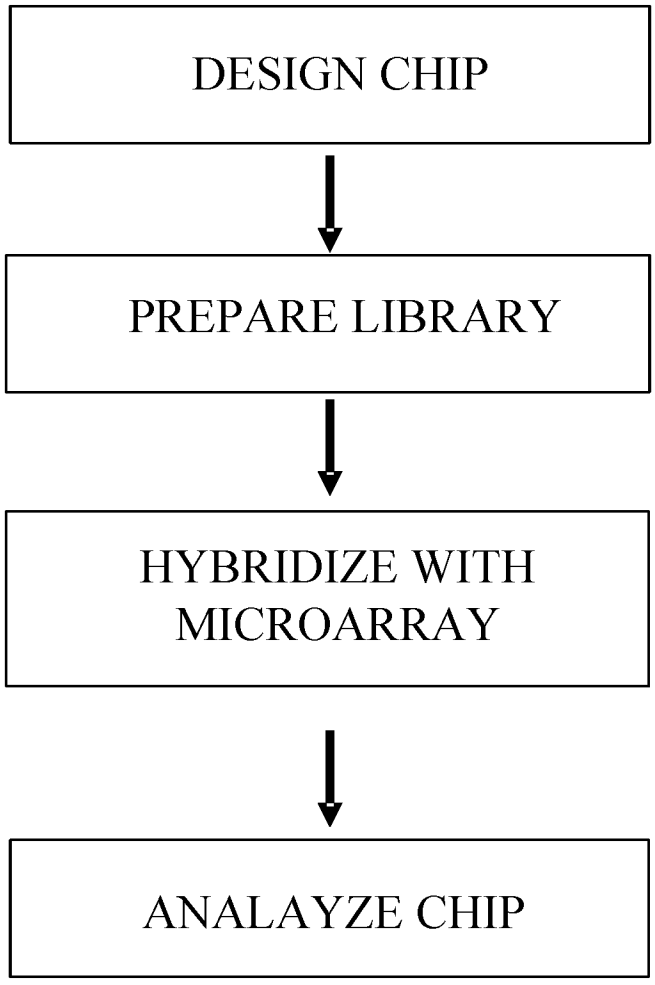

DESIGN CHIP
PREPARE LIBRARY
HYBRIDIZE WITH MICROARRAY
ANALAYZE CHIP

FIG. 26B

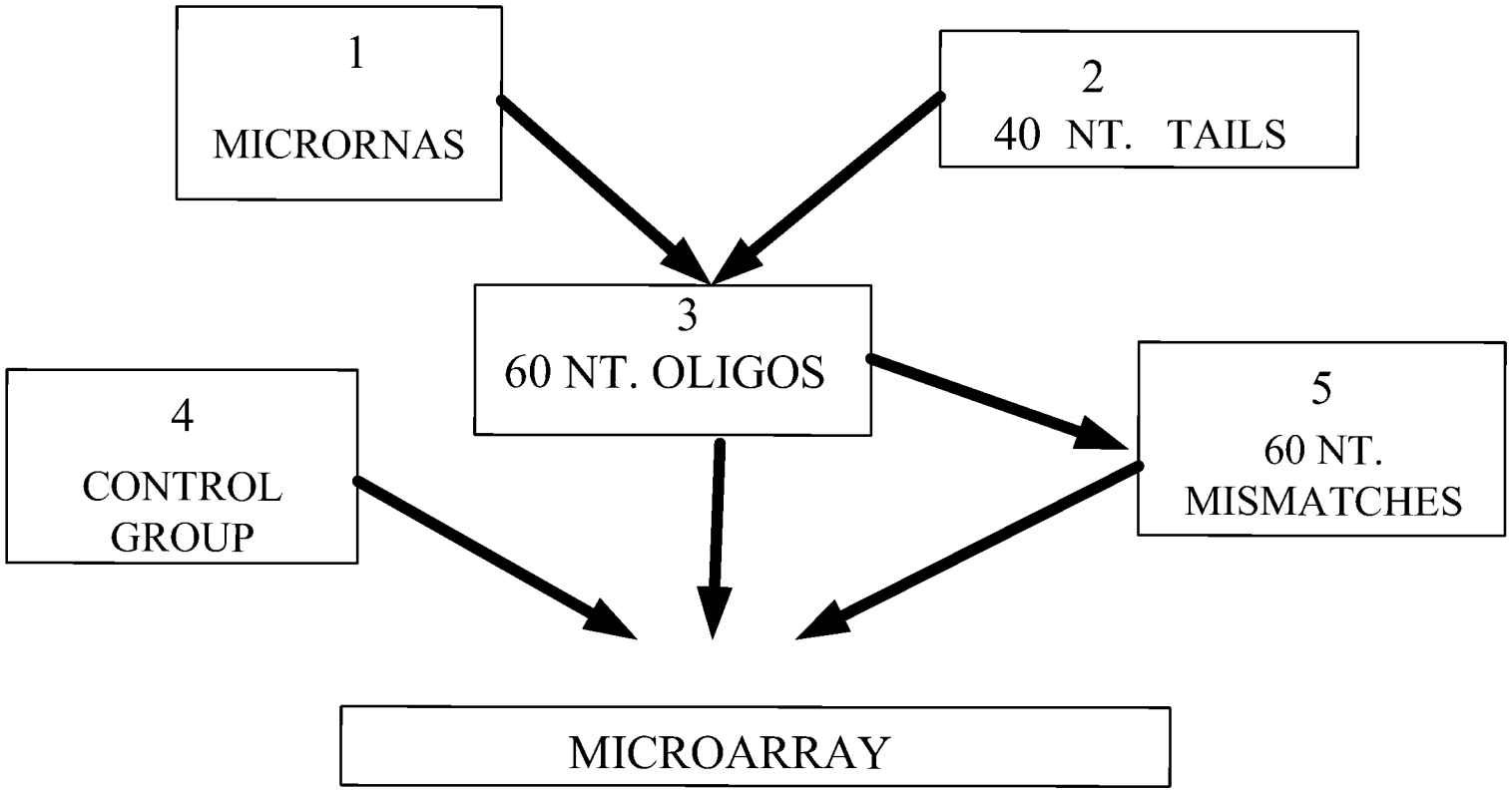

1
MICRORNAS
2
40 NT. TAILS
3
60 NT. OLIGOS
4
CONTROL GROUP
5
60 NT. MISMATCHES
MICROARRAY

FIG. 26C

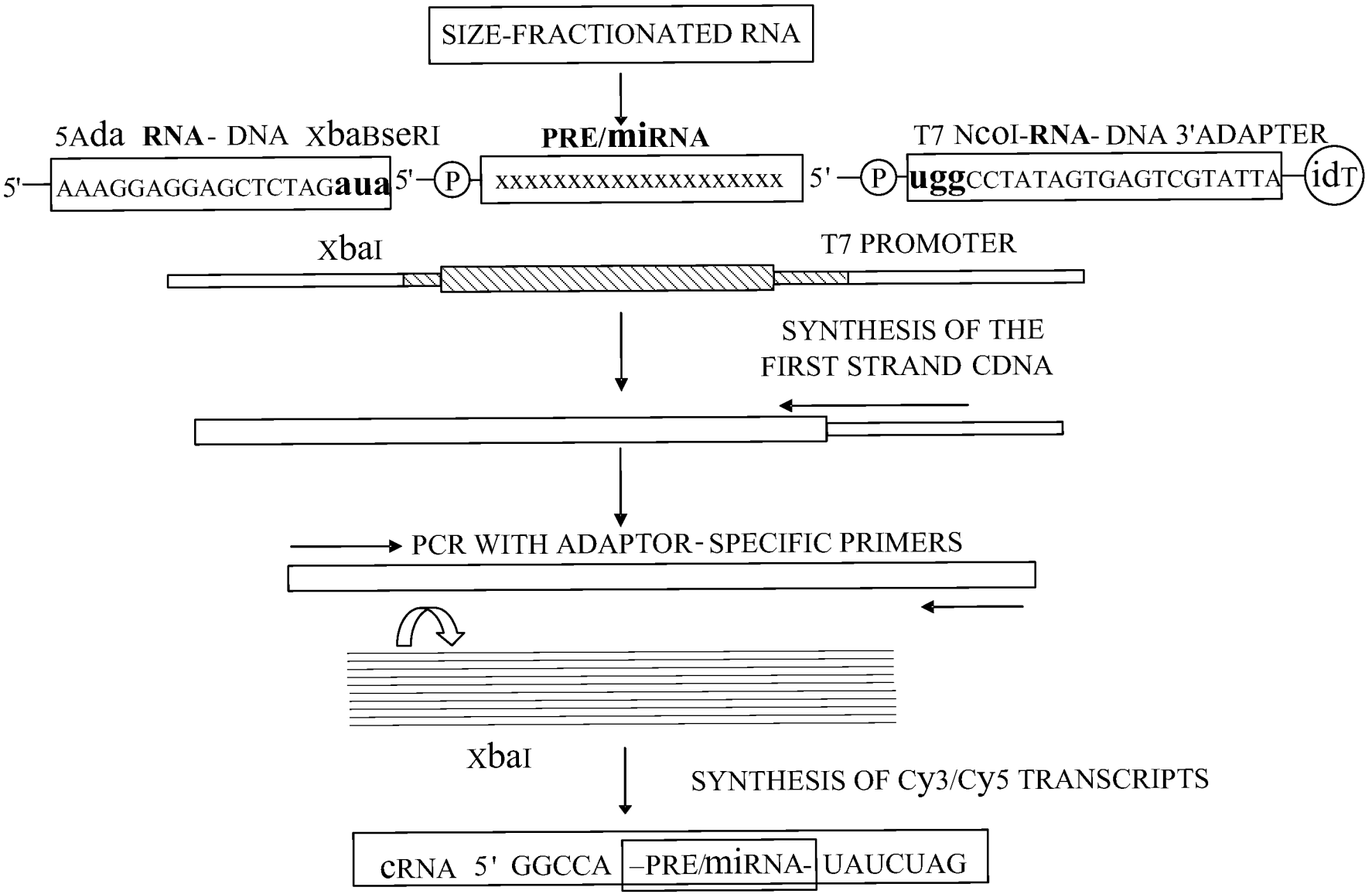

SIZE-FRACTIONATED RNA
5Ada RNA- DNA XbaBseRI
PRE/miRNA
T7 NcoI-RNA- DNA 3'ADAPTER
5'
AAAGGAGGAGCTCTAGaua
5'
P
xxxxxxxxxxxxxxxxxxxx
5'
P
uggCCTATAGTGAGTCGTATTA
idT
XbaI
T7 PROMOTER
SYNTHESIS OF THE
FIRST STRAND CDNA
PCR WITH ADAPTOR-SPECIFIC PRIMERS
XbaI
SYNTHESIS OF Cy3/Cy5 TRANSCRIPTS
cRNA 5' GGCCA –PRE/miRNA- UAUCUAG

FIG. 27A

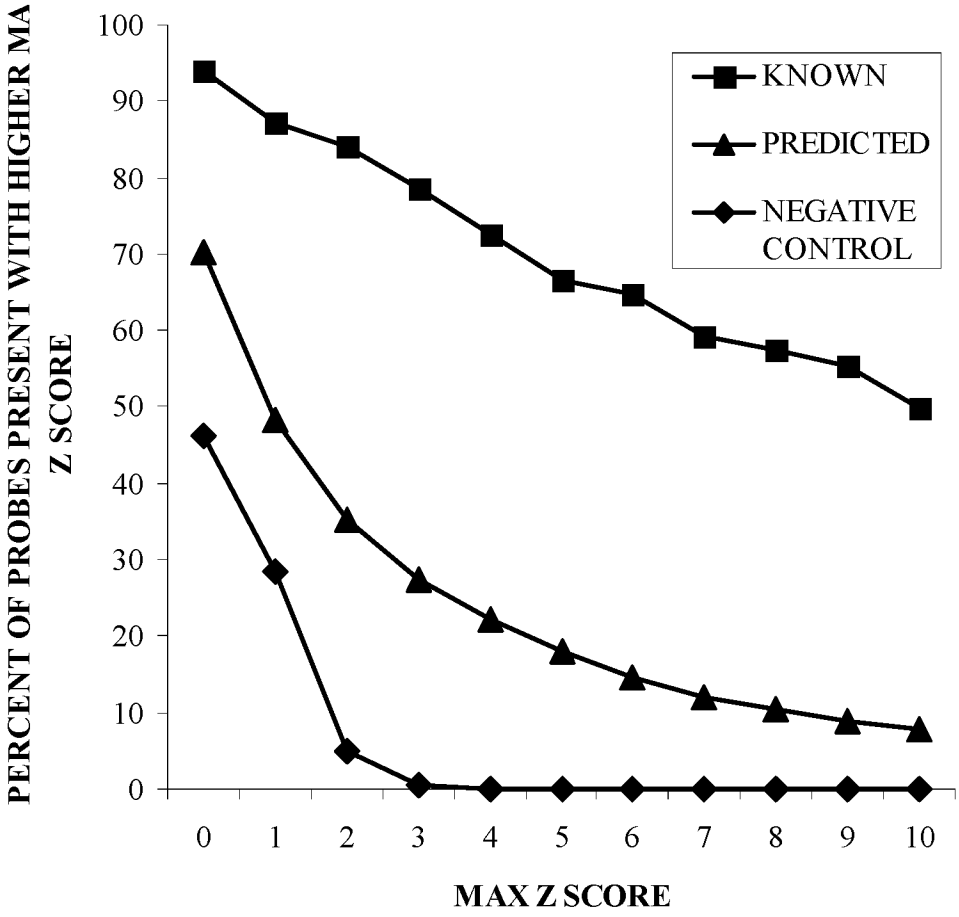

PERCENT OF PROBES PRESENT WITH HIGHER MA Z SCORE
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
MAX Z SCORE
KNOWN
PREDICTED
NEGATIVE CONTROL

FIG. 27B

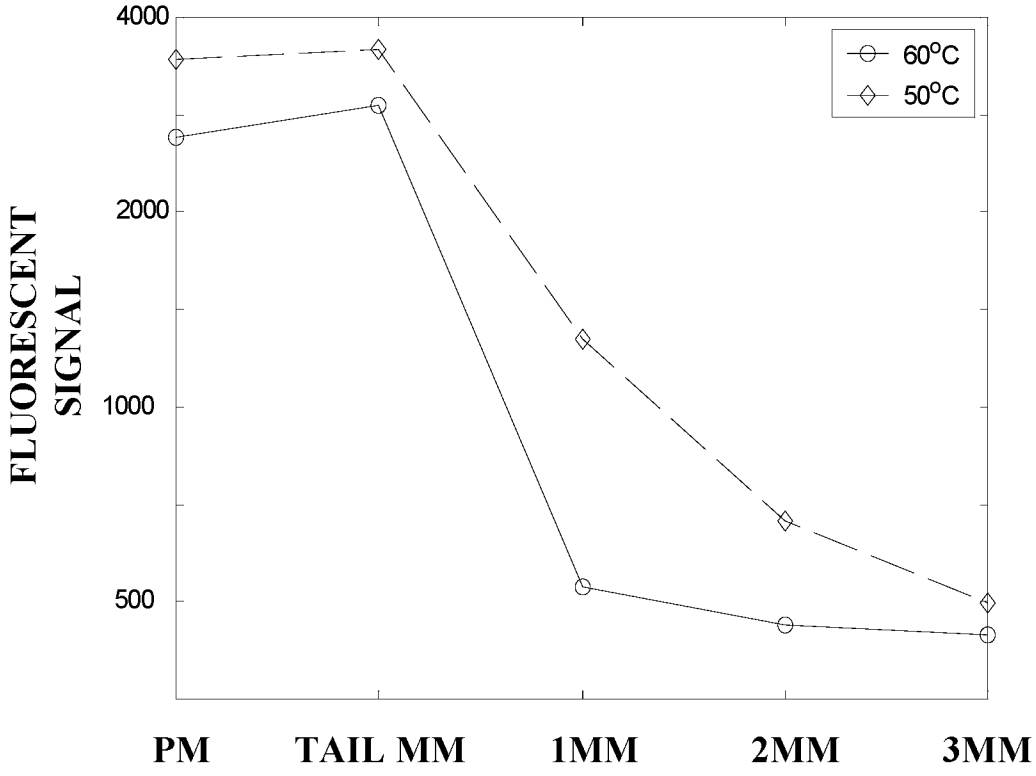

4000
2000
1000
500
FLUORESCENT SIGNAL
60°C
50°C
PM
TAIL MM
1MM
2MM
3MM

FIG. 27C

MIRNA NAME	HELA	BRAIN	LIVER	THYMUS	TESTES	PLACENTA	REFERENCE
HSA-MIR-124A	1879	**65517**	7025	3099	2672	2498	1,3
HSA-MIR-9	642	**42659**	3504	4455	4485	2313	2,3
HSA-MIR-128A	2015	**27701**	4940	4876	5166	2495	3
HSA-MIR-129	503	**22573**	1175	2213	5364	2017	3
HSA-MIR-128B	1168	**21969**	3954	4819	5383	2027	
HSA-MIR-122A	1051	447	**65518**	2644	617	570	1,3
HSA-MIR-194	501	910	**65518**	4737	2342	7952	3
HSA-MIR-148	413	620	**38436**	5250	6204	2711	
HSA-MIR-192	452	606	**20650**	1628	1263	2607	
HSA-MIR-96	887	3100	1477	**44800**	2266	5466	
HSA-MIR-150	648	1463	5295	**65518**	**29728**	5280	
HSA-MIR-205	551	615	1646	**65518**	2645	**39072**	
HSA-MIR-182	662	1944	1091	**25771**	2034	3683	
HSA-MIR-183	1026	1123	1286	**8754**	1681	2138	
HSA-MIR-204	525	3898	1757	6535	**64859**	6233	
HSA-MIR-10B	410	433	477	3871	**23083**	738	
HSA-MIR-154	438	733	1914	3309	**14750**	9637	
HSA-MIR-134	448	617	698	763	**2250**	997	
HSA-MIR-224	3233	11061	7684	**32305**	5377	**65518**	
HSA-MIR-210	844	2280	10703	6864	15288	**62452**	
HSA-MIR-221	625	9325	3520	**20212**	10608	**54287**	
HSA-MIR-141	696	805	1220	4063	2000	**46845**	
HSA-MIR-23A	1312	3492	2990	6021	11173	**40076**	
HSA-MIR-200C	556	595	1027	10636	1478	**33532**	
HSA-MIR-136	465	725	709	776	3100	**8840**	

1 LAGOS-QUINTANA ET AL., CURRENT BIOLOGY 12:735 (2002)

2 KRICHEVSKY ET AL., RNA 9:1274 (2003)

3 SEMPERE ET AL., GENOME BIOLOGY 5:R13 (2004)

FIG. 28A

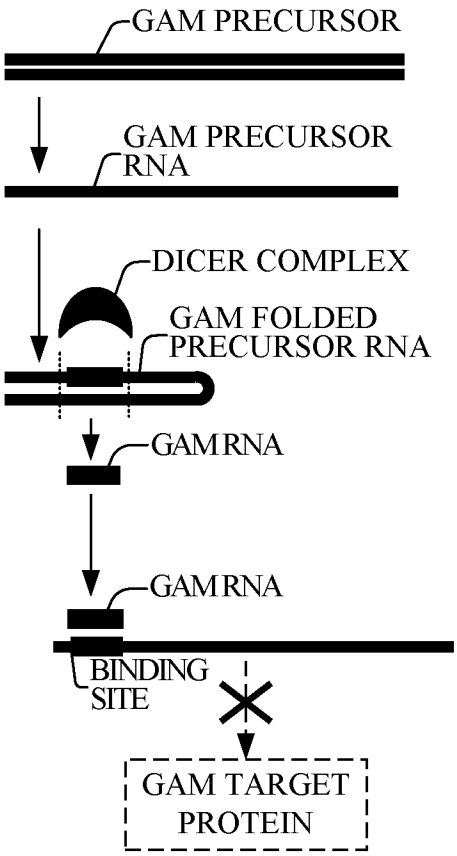


FIG. 28B

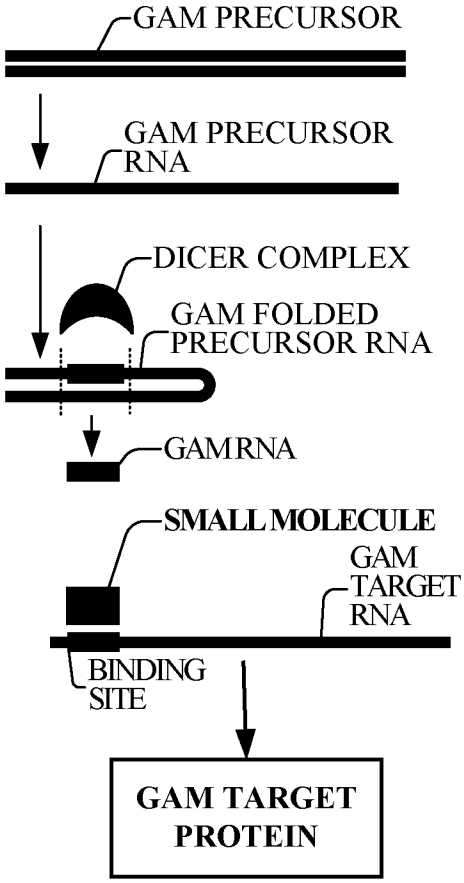


FIG. 28C

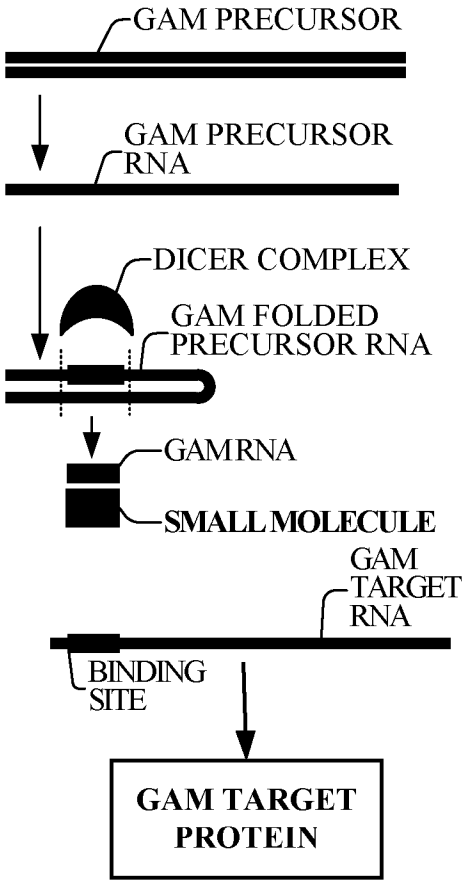


FIG. 28D

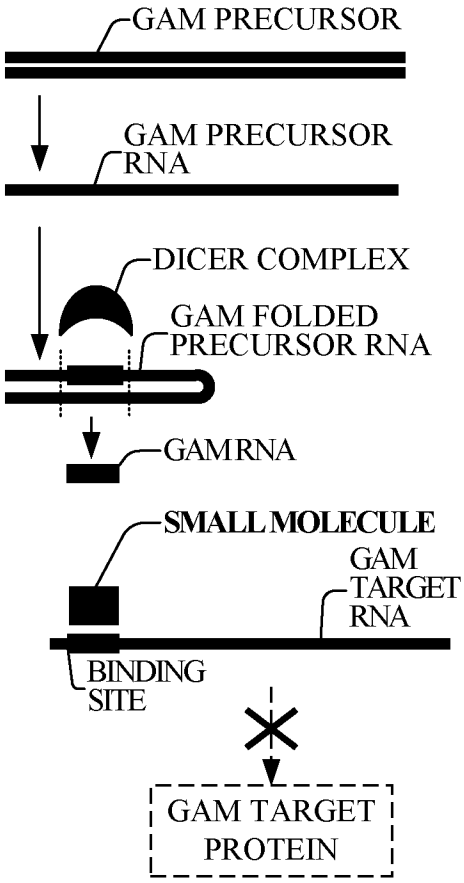
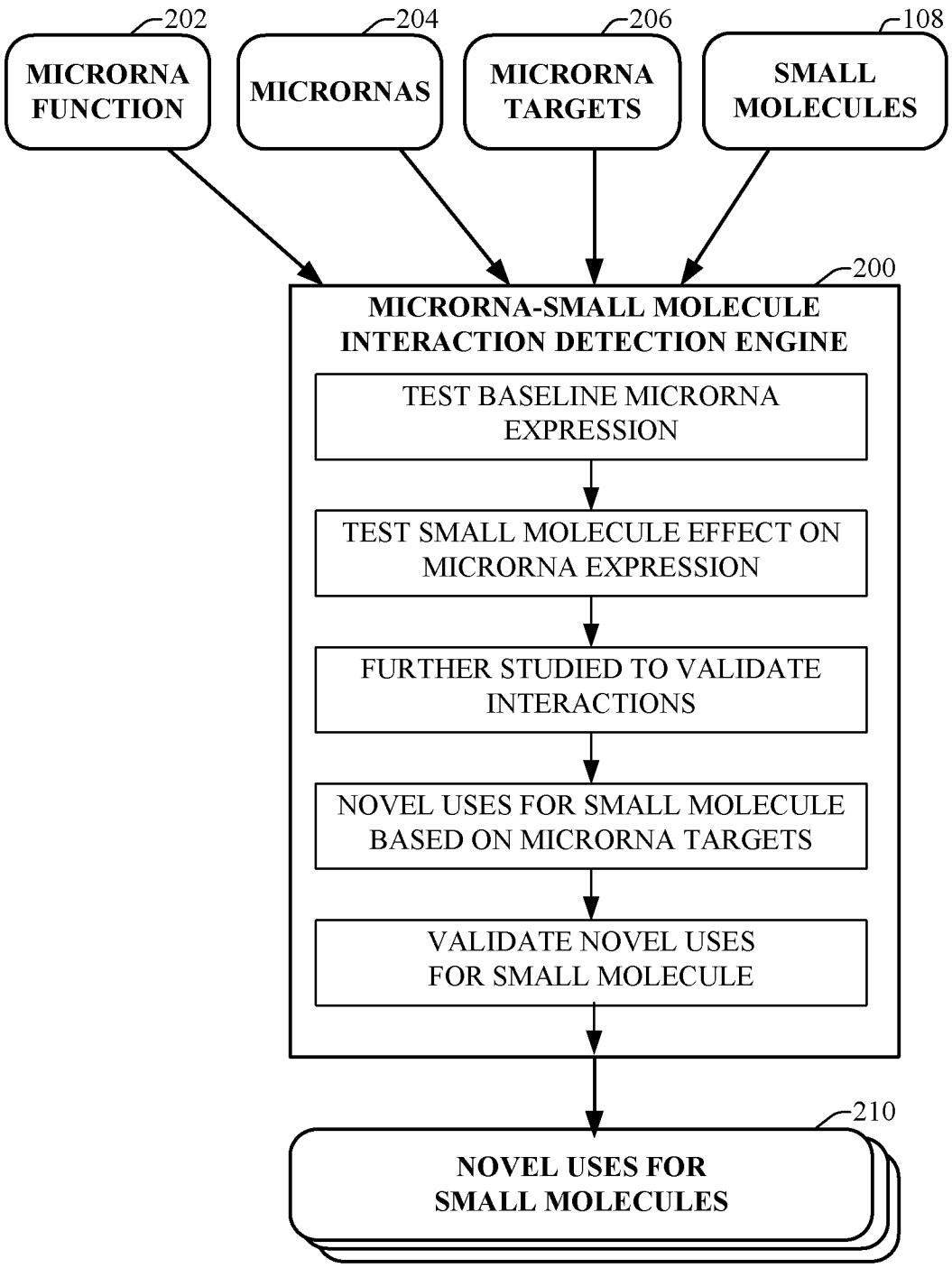


FIG. 29


202
MICRORNA FUNCTION
204
MICRORNAS
206
MICRORNA TARGETS
108
SMALL MOLECULES
200
MICRORNA-SMALL MOLECULE INTERACTION DETECTION ENGINE
TEST BASELINE MICRORNA EXPRESSION
TEST SMALL MOLECULE EFFECT ON MICRORNA EXPRESSION
FURTHER STUDIED TO VALIDATE INTERACTIONS
NOVEL USES FOR SMALL MOLECULE BASED ON MICRORNA TARGETS
VALIDATE NOVEL USES FOR SMALL MOLECULE
210
NOVEL USES FOR SMALL MOLECULES